STUDIES

FROM

THE BENDER

Hygienic Laboratory

ALBANY, N. Y.

REPRINTS

Volume II

1905

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NOTE

* *

THIS volume comprises the publications of the Bender Hygienic Laboratory for the year 1904-'5. These have appeared in various medical journals, but for the sake of uniformity in paper and press work, the reprints have been taken from the Albany Medical Annals. The object of again presenting these studies is to bring them in collected form before those especially interested in the laboratory or its work.

RICHARD M. PEARCE,
Director.

THE BENDER HYGIENIC LABORATORY
ALBANY, N. Y., *January*, 1906.

CONTENTS

* *

PAGE

I. Experimental Cirrhosis of the Liver. (Plate III) . 11
Richard M. Pearce, M.D.

II. Experimental Arteriosclerosis. (Plates I and II) 21
Richard M. Pearce, M.D. and
Edwin MacD. Stanton, M.D.

III. The Sequence of the Pathologic Changes in Appendicitis 33
Edwin MacD. Stanton, M.D.

IV. Primary Carcinoma of the Veriform Appendix, with a Report of Three Cases 45
Leon K. Baldauf, M.D.

V. Retention Cyst and Diverticulum of the Veriform Appendix (with one illustration) 59
Erastus Corning

VI. The Elimination of Endogenous Uric Acid in a Case of Chronic Gout (with one illustration) 75
Arthur T. Laird, M.D.

VII. Malignant Ovarian Tumors in Children with Report of a Case 89
J. Lewi Donnhauser

VIII. Actinomycosis Limited to the Urinary Tract . . . 101
Edwin MacD. Stanton, M.D.

IX. Annual Report of the Director 107

Reprinted from ALBANY MEDICAL ANNALS, February 1906.

EXPERIMENTAL CIRRHOSIS OF THE LIVER.*

By RICHARD M. PEARCE, M. D.

(From the Bender Laboratory, Albany, N. Y.)

(Plate III.)

The experimental studies upon which this communication is based were suggested by an investigation[1] of the necroses occurring in the liver of the dog as the result of the intravenous injection of haemolytic immune sera. These necrotic lesions, which appear to have a very definite relation to thrombi composed of fused red blood corpuscles, vary in position and extent according to the amount of serum administered. Small doses cause focal lesions more or less isolated and irregularly distributed; large doses produce a diffuse necrosis which spares only the tissue about the larger portal spaces. The uniformity and extent of this latter lesion suggested the importance of studying the repair process which naturally follows it in those animals surviving the acute toxic effects of the serum. It was evident that the extent of the injury was such as to preclude complete repair by the regeneration of liver cells alone. If then, the defect were to be repaired by connective tissue proliferation the resulting histological picture would, except for a difference in the distribution of the new tissue, closely resemble cirrhosis in man.

Experiments based on this method have not, heretofore, been made. Joannovics,[2] alone, of the few investigators who have studied the lesions of the liver due to haemolytic sera, has described repair about foci of necrosis. Flexner,[3] in 1894, while studying the lesions occurring in the organs of the rabbit after the injection of dog's serum observed a well marked cirrhosis due apparently to repair about multiple necroses. The lesion was found, however, but once and could not be reproduced in other animals. The literature contains, as far as I am aware, no other references to similar lesions due to serum injections.

Methods.—Dogs were injected either in the smaller branches of the femoral vein or in the abdominal cavity with serum obtained from rabbits which had received repeated injections of the red blood corpuscles of the dog. The dose usually employed was one cubic centimetre of serum to 500 to 1000 grammes of body weight. The majority of the animals died within forty-eight hours; those which survived were killed at intervals varying from forty-eight hours to thirty-six days.

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* This study has been conducted under a grant from the Rockefeller Institute for Medical Research. Read before the American Association of Pathologists and Bacteriologists, Chicago, April 19, 1905. Published also in *The Journal of Experimental Medicine*, 1906. viii, 64.

Character of the Primary Necrosis.—The necrotic lesions in the liver vary according to the dose of the serum. As the etiology and the general character of the focal necroses have been discussed elsewhere, only the more extensive form of necrosis, which, through an equally wide-spread process of repair leads to cirrhosis, will be considered at this time. The macroscopic appearance of the liver in animals dying within a few minutes or hours after injection is that of intense congestion. Microscopically, the vessels are found to be distended by closely massed red blood corpuscles. The coalescence of red cells is very evident in the portal veins; while in the capillaries the occlusion leads to a distension so great that the columns of liver cells are more or less obscured. This congestion is less evident about the larger portal spaces. After twenty-four to forty-eight hours, the liver presents a uniformly mottled appearance; fine irregular yellowish brown or greyish yellow non-elevated areas being sharply separated from deeply congested or occasionally even haemorrhagic areas. On section the brownish portions have a distinct hyaline appearance. The superficial portions of the liver are uniformly more extensively involved than are the deeper portions though in some of the smaller lobes the necrosis may be quite general. Histologically, the necrosis, which is hyaline in character, involves all portions of the liver tissue except circular areas of varying size in the immediate neighborhood of the larger portal spaces (see Fig. 1).

In the necrotic areas the destruction, as far as the hepatic cells are concerned, is uniform and complete; the cells of the capillaries may, however, persist. A narrow ring of liver cells with vacuolated protoplasm and pyknotic nuclei separates, as a rule, the necrotic from the normal tissue. Leucocytic infiltration may or may not be present. The capillaries of the necrotic tissue are widely dilated and tightly packed with swollen and distorted red blood corpuscles which may occur in masses or may retain distinct outlines. In the congested portal veins on the other hand the fusion is quite constant, the plugs for the most part having a distinctly hyaline appearance. The perivascular spaces of the capillaries are distended with serum and the bile passages of all sizes are, as a rule, dilated and engorged with bile.

The cause of the necrosis is an obstructive congestion of the capillaries and the smaller branches of the portal vein by fused masses of red cells. To the effect of this obstruction, essentially a thrombosis, is added the pressure exerted by the perivascular oedema and the over-filled bile capillaries. In portions of the liver midway between the larger portal spaces these factors are sufficient to overcome the pressure in the capillaries from the hepatic artery and necrosis results; the cells in the neighborhood of the larger portal spaces, on the other hand, are preserved through a better supply dependent, presumably, upon the greater arterial pressure in this region.

A review of the literature of infarction of the liver in man and of experimental infarction shows no condition analagous to that here described; nor are any of the theories put forth concerning the etiology of infarction applicable to it. A possible exception is the wide-spread haemorrhagic infarction produced by Wooldridge[4] as the result of injecting into the jugular vein of the dog a complex proteid substance derived from the thymus and other glandular organs. The infarctions were associated with thrombi in the branches of the portal vein and in this regard as well as in the character of the necrosis, Wooldridge's lesion resembles that just described. Moreover, in animals which survived fourteen days, he observed scattered foci of repair resembling early cirrhosis. He does not consider the thrombosis alone to be sufficient cause for the necrosis, but believes that an important adjuvant is some change in the chemical composition of the blood caused by the proteid substance injected.

*The Reparative Process.**—Only fifteen of forty-three animals survived the acute effects of the serum a sufficient length of time to allow repair of the liver lesion to take place. The liver of each, however, shows some stage of repair, and as various periods from thirty-eight hours to thirty-six days are represented, it has been possible to study all stages of the development of the cirrhotic lesion.

At thirty hours the first and only evidence of repair is karyokinesis of the liver cells. This, however, is not conspicuous and the mitotic figures are found only after prolonged search. They occur, uniformly, not at the edge of the necrotic tissue, but in liver cells two or three rows removed. Mitotic figures have never been seen earlier than thirty-eight hours, and at this period in but one animal.

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* Only a general outline of the reparative process will be given at this time; the details of the finer changes and their interpretation will be presented in a future communicaton on the repair of liver tissue.

The period from forty-eight to sixty hours is represented by five animals. The character of the repair is the same in all, but some difference in degree is evident. The most striking feature is the proliferation of the endothelial cells. These surround the necrotic tissue and penetrate it from every side. Similar cells corresponding to the remains of the capillaries may be seen in some places within the necrotic areas. Many of these cells have irregular nuclei suggestive of mitosis, but a definite karyokinetic figure, in a cell surely endothelial, was found at this stage but once; and this was in the liver of an animal killed exactly forty-eight hours after injection. The endothelial cells show a tendency to surround small fragments of necrotic liver cells and occasionally they contain one or two red blood corpuscles. Leucocytic infiltration occurs to a very slight extent.

By the end of the fourth day the proliferation has advanced so rapidly that the bulk of the necrotic tissue has been replaced. Within the necrotic areas the bands of new tissue are more definite. Mitotic figures in liver cells are so numerous that three or four may be found in one field of a one-twelfth lens. A few lymphoid cells are seen in the portal spaces.

The picture at the fifth day differs only in the extent of the process. The new tissue has assumed all the characteristics of granulation tissue and contains giant cells which surround fragments of hyaline material. The first suggestion of intercellular fibrillæ is seen at this stage.

The later stages from the eleventh to the thirty-sixth day illustrate the gradual transformation of this young granulation tissue into a very definite connective tissue. At the eleventh day the new blood vessels are very prominent and the fibrillated character of the connective tissue well marked. All stages after the fourth day show a few scattered lymphoid cells, but this has not been a prominent feature except in one animal, killed on the twenty-fifth day, in which the tissues of the portal spaces were filled with lymphoid and plasma cells.

The oldest as well as the most typical lesion was that found in an animal killed on the thirty-sixth day (see Fig. 2). Microscopically, the liver was much firmer than normal, had a finely granular surface, and was deeply bile stained. The capsule showed irregular areas of thickening and was mottled by an ill-defined congestion. On section a distinct pseudo-lobulation was evident; definite islands of brownish yellow liver tissue being marked off by a fine greyish network of newly-formed tissue. Histological examination shows broad bands of connective tissue entirely replacing the necrotic areas and forming a uniformly arranged network separating the surviving islands of liver tissue about the larger portal spaces. The new tissue is distinctly fibrous and contains many newly formed blood vessels and bile ducts; it stains deeply by Mallory's connective tissue method. The formation of new liver cells is still demonstrable. Fragments of necrotic hyaline cells, not infrequently partially calcified, are found in the midst of the new connective tissue. Large irregular multi-nucleated masses of protoplasm surround these and are apparently active in englobing and removing them. These multinucleated cells, essentially foreign body giant cells, are derived in part from endothelial cells and in part from liver cells. Associated with them are numerous multinucleated liver cells without inclusions. Lymphoid and plasma cells are present, but only in small numbers.

Discussion.—The final stage of the lesion herein described, constituting as it does a chronic interstitial hepatitis of diffuse, but uniform distribution, may justly be termed an experimental cirrhosis. No close analogy, however, can be drawn between it and human cirrhosis, for, with the possible exception of the so-called central cirrhosis associated with chronic passive congestion, a form of interstitial hepatitis with similar distribution of the new tissue does not occur in man. In this connection Bostreom's[5] recent discussion of liver cirrhosis as a repair process in chronic passive congestion is of especial interest. As the result of a study of material from man he reaches the conclusion that the congestion causes destruction of liver cells not necessarily by pressure of the widened capillaries, but through nutritive and functional disturbances. With these conditions are associated rupture of the capillary wall and the escape of red cells into the perivascular lymph spaces. Thrombosis also is not an infrequent occurrence and has a close relation to the destruction of liver cells. The repair, which is most active in the region of the portal spaces, results in a very definite cirrhosis. When one considers that the necrosis in my experimental lesion is preceded by an intense congestion associated with all the etiological factors described by Bostroem, the analogy of the repair lesion to the cirrhosis which he describes becomes very apparent. Comparisons as to the etiology of cirrhosis in general are not justifiable, for we know of no toxic substances associated with abnormal conditions in man which are capable of causing the wide-spread necrosis seen in these experimental lesions. The only condition comparable is acute yellow atrophy with which the early necrotic and reparative lesions of the second to the sixth day have much in common.

On the other hand, however, these experimental lesions demonstrate that a cirrhosis may follow extensive primary destructive lesions and thus support the theory of Kretz[6] that cirrhosis is essentially a reparative process. Kretz, who bases his conclusions on an extensive study of the disease in man, believes cirrhosis to be the result of successive processes of repair following repeated focal injuries of the liver parenchyma. The primary lesion is, he thinks, a destruction of groups of liver cells at the periphery of the lobule. After such destruction the uninjured cells of the lobule, as well as the cells of the bile ducts, proliferate in an attempt to repair the injury. The continued occurrence of degeneration and regeneration causes the formation of new connective tissue which eventually atrophies thus leading to the picture seen at autopsy. Cirrhosis, therefore, is the result of repeated localized destructive lesions from which the liver has more or less recovered. This view it will readily be seen accepts Weigert's[7] opinion that the primary lesion in all interstitial new growth of tissue is cell death and also includes Kirikow's[8] opinion that in addition to cell death the continual action of the toxic substance is necessary; but adds the important factor of continuous regeneration.

W. G. MacCallum's[9] study of the regenerative changes in human cirrhosis strongly supports the theory of Kretz as do also the studies by McPhedran and A. B. MacCallum,[10] Meders,[11] Marchand,[12] Stroebe,[13] Barbacci,[14] W. G. MacCallum[15] and others of repair in acute yellow atrophy of the liver.

The experimental studies of repair after various mechanical injuries also indicates the ease and rapidity with which liver parenchyma repairs loss of substance. From the observations of Podwyssozki[16] and Ponfick,[17] it is seen that slight injuries are repaired by the proliferation of either liver cells or the smaller bile ducts; connective tissue repair occurring only when loss of substances exists. Of special interest is the true hyperplasia observed by Ponfick and by v. Meister[18] after extirpation of large portions (one-quarter to three-quarters) of the entire liver.

On the other hand the argument is presented that focal necrotic lesions of the liver frequently occur in man without repair either by proliferation of parenchymatous cells or by formation of connective tissue. In this connection the liver lesions of typhoid fever, diphtheria and other acute infections as well as various experimental infections of animals are quoted. It is probable, however, that in such cases the reparative power of the cells is in some way delayed, or consists possibly of a true regeneration of liver cells without the proliferation of connective tissue; for in hog cholera, in which above all other diseases, necroses of the liver are most abundant and widespread, cirrhosis of the liver commonly occurs. Salmon, Smith and Kilborne,[19] in the study of hog cholera in an epidemic including both acute and chronic cases, found well marked cirrhosis in about half of the animals examined.

The question as to whether the interstitial tissue or the parenchyma is primarily affected in cirrhosis receives little enlightenment from the literature of experimental cirrhosis. Heukelom,[20] who reviewed the literature up to 1896, collected nineteen different methods said to be capable of producing cirrhosis and to these Joannovics[21] in a recent summary adds others. None, however, produce a lesion analagous to that occurring in man. These methods may readily be divided into two groups. In the first we have procedures essentially mechanical in nature, as ligation of the ducts or vessels of the liver, the injection of irritating substances into the ducts or directly into the liver substance, and their application to its surface. The second group includes the administration by the mouth, or by subcutaneous or intravenous injection, of various toxic substances. As a general rule the mechanical methods lead to a more or less irregular connective tissue formation, sometimes with considerable sclerosis, but the lesion under these circumstances is more of an atrophy than a cirrhosis. The toxic agents, for which positive results have been claimed, have been introduced so that they reach the liver through the blood stream. The lesion attributed to such substances is usually described as a primary degeneration of the liver cells with a slight increase of connective tissue, limited as a rule, to the portal spaces; in a few instances a definite perilobular growth of connective tissue, independent of parenchymatous degeneration, has been described. Few of these lesions, however, even in their final stages are comparable to the cirrhosis of man and in none has it been possible to follow step by step the development of a lesion which could probably be termed an experimental cirrhosis.

Summary.—The reparative process which follows the widespread necrosis of the dog's liver caused by the injection of hæmagglutinative serum constitutes a chronic interstitial hepatitis of definite and constant character. This is not only a new type of experimental liver lesion, but is more definitely a cirrhosis than is any other experimental lesion hitherto described. It is of importance in explaining the histogenesis of cirrhosis, and incidentally various repair processes in the liver; but does not aid in the elucidation of the etiology of cirrhosis in man, nor does it explain the peculiar arrangement of the new connective tissue in any form of human cirrhosis except, possibly that associated with chronic passive congestion. It definitely demonstrates, however, that cirrhosis may follow extensive primary destructive lesions, a view not yet fully accepted, and supports the contention of Kretz that cirrhosis is essentially a reparative process.

EXPLANATION OF PLATE III.

Fig. 1—The primary lesion. Extensive hyaline necrosis sparing only the tissues about the larger portal spaces. Thirty-eight hours. Dose, 1:1000. Methylene blue and eosin. No. 2 oc., No. 3 obj., Leitz.

Fig. 2—Experimental cirrhosis. Broad bands of newly formed connective tissue surround the islands of normal liver about the portal spaces. In the stroma may be seen newly-formed bile ducts and numerous giant cells. Thirty-six days. Dose, 1:1000 Methylene blue and eosin. No. 3 oc., No. 3 obj., Leitz.

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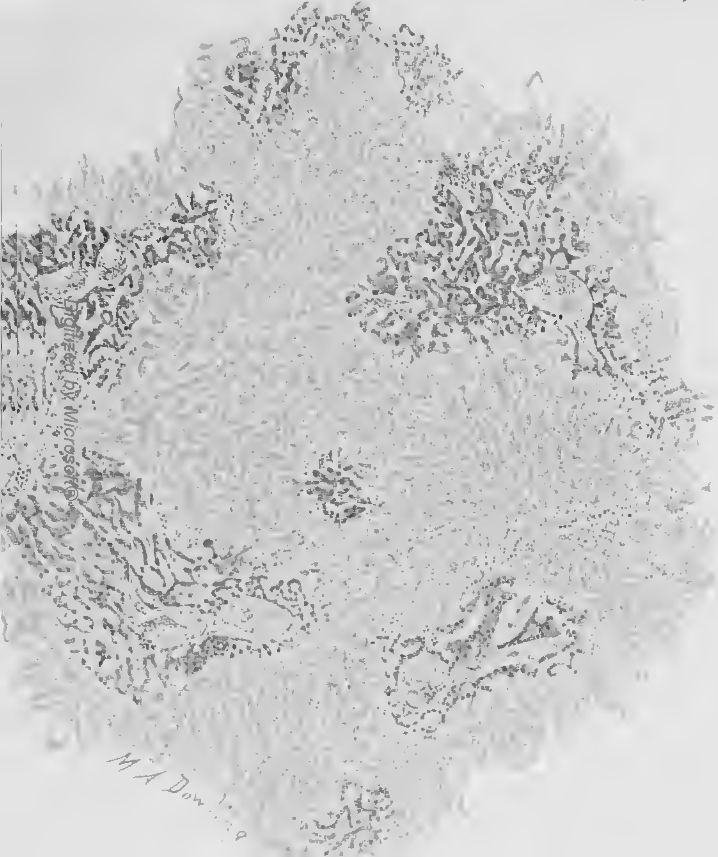
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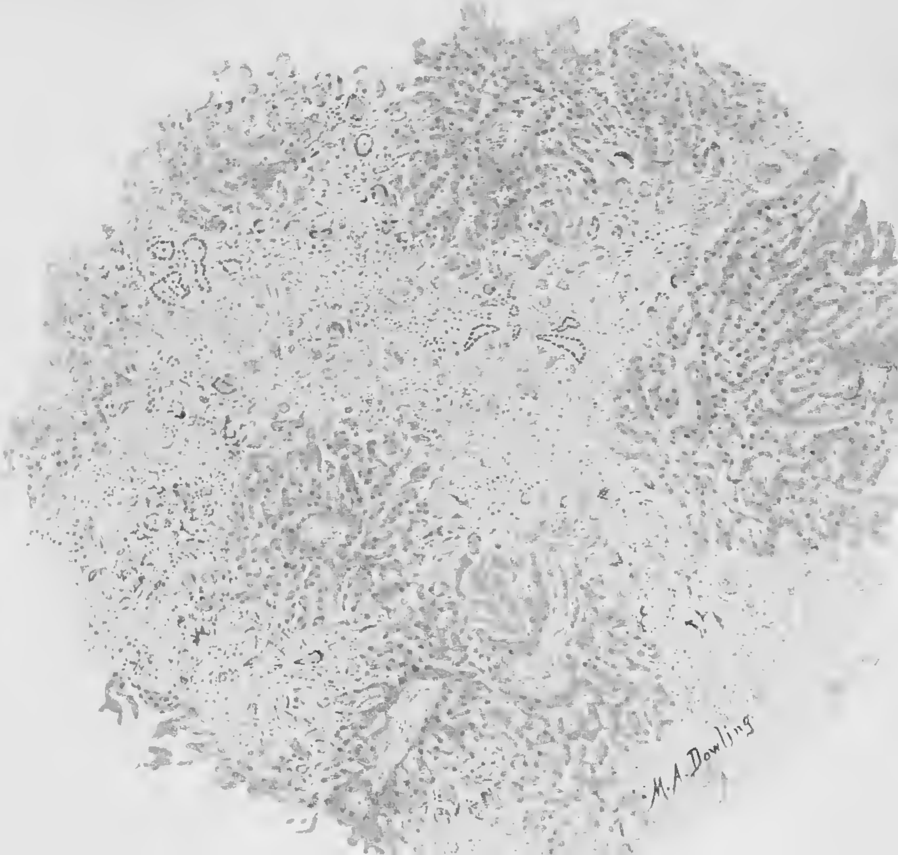
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EXPERIMENTAL ARTERIOSCLEROSIS.[1]

BY RICHARD M. PEARCE, M. D., AND E. MACD. STANTON, M. D.

(From the Bender Laboratory, Albany, N. Y.)

(Plates I and II)

The complexity of the pathologic picture in the arteriosclerosis of man and the difficulty of determining the nature and sequence of the early changes have led many investigators to attempt the experimental production of the disease in the hope of thus solving some of its many confusing problems. Until within the last two years all such efforts have been unsuccessful. It is true that Thoma described a diffuse arteriosclerosis in the dog as the result of a chronic experimental aortic insufficiency and that Gilbert and Lion[1] produced scattered sclerotic and calcareous changes in the vessels of animals by injecting bacteria and their toxins. Thickening of the vascular walls has been described also as the result of poisoning animals with lead. These results, however, have been inconstant and lack confirmation. Jores,[2] in his excellent monograph on arteriosclerosis published in 1903, reached the conclusion, based on a critical review of the literature, that all experimental methods fail to cause lesions similar to those occurring in man. Various endarterial lesions, obliterative or otherwise, as well as diffuse inflammation and atrophy, have been produced by injections of bacteria or their toxins by the application of irritating substances to the perivascular tissues and by ligation and other forms of mechanical injury; but none of these lesions is analogous to true arteriosclerosis.

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[1] This investigation was conducted under a grant from the Rockefeller Institute for Medical Research. Read before the Association of American Physicians, at Washington, May 17, 1905. Published also in *Journal of Experimental Medicine*, 1906, viii, 74.

It is a curious coincidence that in the same year in which Jores reached this conclusion Josué[3] described experimental lesions in the aorta of rabbits, somewhat similar to those of human arteriosclerosis. These were caused by frequent intravenous injections of adrenalin. With the exception of a few inconclusive experiments of Jores, who gave dogs adrenal tablets in their food in the hope of obtaining lesions due to heightened blood pressure, Josué appears to be the first investigator to attempt the experimental production of arteriosclerosis by the use of the principle of the adrenal gland. His results have been confirmed by Erb,[4] Rzentkowski,[5] Fisher,[6] and others. Their reports include but a small group of experiments, and deal for the most part with the late changes, which they describe variously as arteriosclerosis, atheroma, and calcification. The principal histologic changes to which they call attention are alteration in the elastica and the infiltration of lime salts.

The importance of a method capable of producing an experimental lesion so closely resembling human arteriosclerosis is apparent. It allows an opportunity to study many of the obscure problems of the disease, as the nature of the primary changes, the sequence of these changes, and the combinations which constitute the fully-developed lesion. It was with the hope of elucidating some of these problems that the present investigation was undertaken. The results have been satisfactory beyond all expectation. Vascular changes, capable of throwing much light upon the pathology of arteriosclerosis, and also that of aneurysm formation, have been readily produced. Only a general outline of these will be given at this time, for many of the details of the histologic changes, especially of the process of repair, are so important that they require a more extended study. A consideration of these details is therefore reserved for a future publication, based on a second series of experiments now in progress.

METHODS. Rabbits have received in the veins of the ear repeated injections of a 1:1000 solution of adrenalin. The solution was prepared by a chemist, with due regard to asepsis and chemical purity. Physiologic salt solution was used as a medium. In addition to adrenalin (Parke, Davis & Co.) it contained chloretone in the proportion of one-half of one per cent. and a sufficient amount of hydrochloric acid to make the solution faintly acid.

An initial dose of three minims[1] and the repetition of the same amount every other day has been the usual procedure, though in some experiments the dose has been gradually increased. Not infrequently the early injections cause death from acute dilatation of the heart and pulmonary edema. Such accidents usually occur after any one of the first seven or eight injections. If the animal survives this period it appears to gain a certain amount of immunity, or, at least, tolerance to adrenalin, so that the dose may be gradually increased during several weeks, until twenty to twenty-five minims may be given every day. This increased resistance to adrenalin has been noted also by Erb and Fisher. The animals have been killed after periods varying from a few days to eight and a half weeks.

For histologic study tissues have been preserved in Zenker's fluid, alcohol and six per cent. formalin; imbedded in celloidin; and stained with hematoxylin and eosin, and by Weigert's elastica and Mallory's connective-tissue methods. The scharlach R. and Osmic acid methods have been employed for the demonstration of fat. Sections hardened in Flemming's solution and stained by hematoxylin have been found to be most satisfactory for purposes of general study. By this method the nuclei and areas of calcification stain blue; fat, if present, black. The elastic fibres stand out prominently as light, greenish-yellow, glistening lines, while all other structures are of a faint gray color.

Results. Of twenty animals receiving adrenalin nine succumbed to the acute effects of the drug within fifteen days. These nine represent animals receiving one, three, four, five, seven, and eight injections of adrenalin on alternate days. In some instances death resulted within a few minutes after the injection, in others, after a few hours. The immediate effect of the intravenous administration of adrenalin is collapse with difficult and rapid respiration. The animal lies on its abdomen, with legs outstretched, and head resting on the table or raised in spasmodic respiratory effort. Death, preceded by severe convulsive movements, may occur immediately. Other animals recover from the immediate manifestations only to succumb after a few hours. Upon postmortem examination the usual picture is acute dilatation of the heart and edema of the lungs, with, not infrequently, small hemorrhages beneath the pleura and pericardium. In one animal hemorrhages were also found in the adrenal. These acute lesions indicate a very serious disturbance in the terminal vascular territories, and are worthy, perhaps, of further investigation; but as our problem has to do only with the histologic changes in the larger vessels, its scope has been limited to that extent. The theoretic conclusions to be drawn from experimental adrenalin edema and their possible application to acute edema of the lung in man have recently been discussed by Josué.[7]

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[1] Throughout this report the dose will be given in minims. It would be better, perhaps, to use the values of the metric system, but as Josué and others give the dose in minims or drops, we have for purposes of control used the same system of measurement.

In but two of this group of nine animals were changes in the vessels demonstrable. These will be discussed later.

The second group of eleven animals represents those receiving from eight to twenty-eight injections during periods varying from sixteen to fifty-nine days. One of these died on the twenty-fifth day from spinal hemorrhage; another on the forty-sixth day, from unknown cause, three weeks after the cessation of injections; the remaining ten were chloroformed. The aorta in six of these showed marked gross lesions; in the other five it was negative, both macroscopically and microscopically. It is of interest that these five animals were all from the same litter, and each weighed about 750 grams at the time of the first injection. Pic and Bonnamour[8] have come to the conclusion that it is impossible to produce vascular lesions by adrenalin in rabbits weighing less than 2000 grams, and quote in support of this opinion their negative experiments with animals weighing about 1200 grams. That this is not an absolute rule is shown by the fact that the most characteristic and advanced lesions in our series occurred in an animal weighing 870 grams at the beginning and 1020 at the end of the experiment. Otherwise, however, our experience with small animals supports the contention of Pic and Bonnamour.

Attempts to produce lesions in dogs have been unsuccessful. Both old and young dogs have been used. One of the latter, a puppy 2120 grams in weight, received in the ear vein in one month one hundred thirty minims of adrenalin in doses rising gradually from four to twenty minims. Although respiratory and cardiac disturbances frequently occurred immediately after injection, thus indicating a definite physiologic action of the adrenalin, no evidence of vascular lesions could be found at autopsy or upon microscopic examination.

Gross Lesions. These appear to be limited to the aorta. The involvement of other arteries, as the brachial, carotid, and renal, which Erb describes, we have not found. These lesions in the aorta are most marked in the thoracic portion, and are seldom found below the cœliac axis or in the first portion of the arch. The earliest change in the vessel wall manifest to the naked eye is a faint longitudinal or irregular grayish streak of the intima without thickening. This appearance was seen as early as the ninth day in a rabbit which had received five injections. After eight to fifteen injections, especially if the animal is allowed to live for a week or longer after the last injection, very definite lesions are apparent. These consist of irregular, isolated, or confluent areas, usually slightly depressed, of a pearly gray color and almost constantly calcified. The following protocol illustrates this condition:

Rabbit No. 11. Weight, 2,300 grams. Killed May 2d after injection as follows: March 29th and 31st, 4 minims; April 2d and 4th, 5 minims; April 6th and 8th, 7 minims; April 10th, 10 minims; April 12th, 12 minims; April 14th, 15th and 16th, 15 minims. *Autopsy:* The aorta is distinctly dilated, measuring twelve millimeters in circumference at the arch. Beginning at the origin of the left carotid artery is an irregular patch thirty-seven millimeters long, averaging two and a half millimeters in width, and extending in a spiral course along the aorta for a distance of thirty millimeters so as to completely encircle it. Along this patch the wall of the aorta is slightly dilated. The media is firm, parchment-like and so distinctly calcified that the vessel cracks in several places when the arch of the aorta is straightened. At one side of this large patch are two very small oval areas of similar structure. There is no atheroma or ulceration. All the other organs are entirely negative.

The late lesions occurring after from twenty to twenty-five injections are very well marked. The aorta is more or less distorted, rigid and non-elastic. Irregular dilations alternate with elevated brittle areas of calcification. Distinct ulceration with atheroma is not readily demonstrable. Diffuse calcification is not infrequent and small aneurysmal dilations may be present. The following protocol illustrates the advanced lesions occurring in animals receiving large doses during a considerable period of time.

Rabbit No. 3. Weight, 870 grams. Received first injection of 3 minims in ear vein on November 30, 1904. Similar injections were repeated on alternate days until December 30th, after which date the dose was rapidly increased until it reached 20 minims daily. The animal was killed on January 20, 1905. *Autopsy:* Weight, 1,150 grams. The thoracic aorta measures six millimeters in diameter, is distinctly dilated, irregular in outline, stiff and brittle, although the wall is apparently thinned. This condition extends as far as the cœlic axis, beyond which point the abdominal aorta is apparently normal. On opening the aorta the inner surface of the abdominal aorta above the cœlic axis shows numerous yellowish, slightly raised, calcified patches one to one and five-tenths millimeters in diameter, which in the upper portion of the thoracic aorta become confluent. Except in one of the small patches situated in the upper portion of the abdominal aorta there is no evidence of ulceration. All other organs are negative.

The following description from the protocol of a parallel experiment illustrates the tendency to the formation of small aneurysms:

Rabbit No. 2. The aorta averages three millimeters in diameter except at three places where distinct dilations occur. The first of these begins three centimeters below the origin of the aorta and involves the right anterior wall of the aorta for a distance of two centimeters, giving the appearance of a fusiform aneurysm; the diameter of the aorta at this point is four millimeters. A second dilation, two and five-tenths centimeters in length, occurs in the distal portion of the thoracic aorta and a third involves the abdominal aorta for a distance of one centimeter immediately below the cœlic axis. On section the inner surface of the aorta shows sharply circumscribed saccular dilations, varying from one to two millimeters in depth, and corresponding to the protrusions described above. The walls of these aneurysms contain firm placques of calcareous material. The intervening aorta shows a number of yellowish-white elevated areas one to three millimeters in diameter. The aorta below the dilation at the cœlic axis is macroscopically negative.

Histology. In the group presented by the nine rabbits which died during the first two weeks, the vessels of but two showed histologic changes. These were animals which had received four and five injections, respectively. The first died on the fifth day and the second on the ninth day. Scattered through the middle coat of the aorta in each of these are small longitudinal or occasionally irregular, finely granular foci of degeneration. In these areas no nuclei are visible, and the muscle fibres are transformed into a finely granular, almost hyaline material, which stains deeply with eosin. The exact nature of this change is not readily determined, but as the various methods of demonstrating fatty transformation are negative, and those which differentiate elastic fibres show no change in the staining reaction of the latter, the condition would appear to be a simple necrosis limited to the muscle fibres. The elastic tissue has, however, undergone very characteristic morphologic changes, which are found only in the degenerate areas, and are due, presumably, to mechanical influences. In the normal aorta the elastic fibres have a distinctly wavy or curled appearance, and are definitely separated from one another. In the areas described the fibres lose this appearance and become straightened and closely approximated. They are also swollen and occasionally appear to be fused together. Fracture of the fibres is seldom seen at this stage of the process.

A more diffuse lesion of this character was found in an animal killed on the twenty-fourth day after receiving eleven injections. The changes involve the entire circumference of the vessel, sparing to a certain extent, the innermost and outermost portions of the media. In this central zone few or no nuclei can be found, and the altered tissue presents a uniform, finely granular appearance, relieved only by the glistening lines of the elastic fibres. The latter, by selective stain, are seen to be so closely massed together that individual fibres can be distinguished only with great difficulty. On either side of this zone the less degenerated portions of the media show irregular areas, which take the hematoxylin stain in a manner very suggestive of early infiltration with lime salts. There is, however, no distinct calcification and no fracture of elastic fibres.

Lesions of great interest in comparison with the above were observed in two rabbits which had received the same number of injections, but which were allowed to live for ten and eighteen days, respectively, after the last injection. In the aorta of each are found a few areas of granular necrosis, but for the most part these areas have been altered by infiltration with lime salts. From the topography of the areas of calcification and their relation to the necrotic foci it is evident that the deposition of lime salts follows the necrosis. It would appear, therefore, that the primary degenerative lesions are well advanced by the end of the third week, and that, after this, but one or two weeks' time is sufficient for advanced calcification. The latter may, however, occur much earlier, for in one rabbit, killed on the sixteenth day, small but very definite foci of lime infiltration were present.

In the areas of lighter deposition of lime it is seen that these salts are first deposited between the elastic fibres, an observation which indicates that the destruction of the muscle fibre is the older, and therefore in all probability the primary lesion. In the areas of advanced calcification, although the elastic fibres appear to be completely destroyed by the calcareous transformation, Weigert's stain shows them to be still present, though they stain poorly and are frequently fractured. Not uncommonly at a point of fracture one bundle of fibres overlaps another, the ends being splinted together by an encapsulating mass of lime salts. These fibres are always perfectly straight, except at angles formed by fracture. A definite relation appears to exist between calcification and fracture of the elastic fibres. In areas of the most extensive calcification few breaks in the elastic fibres have been observed, while, on the other hand, they are constantly present in the aneurysmal dilations which show comparatively little calcification.

Lesions of this stage show the first evidence of repair. This is indicated by the collection of newly formed cells about the foci of calcification. These cells are closely massed, surrounded by but a slight ring of protoplasm, and appear to be of connective-tissue origin, though it has been impossible to always distinguish between such and the nuclei of smooth muscle fibres. No accumulation of polymorphonuclear leukocytes, or lymphoid cells, has been seen. Of greater interest are the proliferative changes in the intima. These occur only opposite distinct breaks of considerable depressions in the media, and include proliferation of the lining endothelium and, to a greater extent, the subendothelial tissues. The endothelial cells proliferate to form two or three layers of cells longitudinally arranged, while the subendothelial space, barely visible in the normal aorta, becomes very prominent owing to the presence of closely packed oval nuclei arranged vertically to the lining endothelium. Between the nuclei are delicate, newly formed connective tissue and elastic fibrils. In the late stages the newly formed elastic fibrils are very prominent. In the angle of fracture the nuclei of the media assume a perpendicular arrangement, very striking in contrast to their longitudinal arrangement elsewhere. The entire picture is distinctly that of a compensatory proliferation—an effort to strengthen the weakened point in the vessel wall.

Such are the essential phases of this lesion in the order of their sequence. The more prolonged experiments offer no fundamentally new features, but the combinations of these primary changes in the course of the more extensive involvement of the vessel wall, lead to a complex histologic picture closely resembling advanced human arteriosclerosis. This is seen only in animals which have received gradually increasing doses during a period of seven or eight weeks. The vessel wall becomes greatly thickened, not only by infiltration of lime salts, but also by an extensive repair process, which involves the intima as well as the media. Small foci of complete necrosis, analogous to atheroma and entirely different from the primary degeneration, are also seen in areas in which the elastic fibres are completely destroyed. These present a uniform, finely granular appearance, and stain deeply with eosin. The osmic acid method for fat is negative, but a few fine droplets are evident after treatment with scharlach R. About such areas repair takes place, but it is not as active as it is about the masses of lime salts.

The most striking feature of the late histologic picture is the extent of repair in the intima. The latter, with its newly formed connective tissue and elastic fibrils, becomes so greatly thickened that it constitutes in some places a quarter to a third of the entire vessel wall, and offers convincing evidence of the compensatory nature of the repair process.

It is in these late lesions that the small aneurysms are seen. They occur at points where the elastica is so completely destroyed as to be transformed into an indistinct mass of fractured granular and fused fibres. The transition from normal to necrotic fibres is always sharp and distinct, and marked by complete fracture of all elastic tissue. It is worthy of note that in the thinned wall of these aneurysms the degree of calcification is, as a rule, less marked than eleswhere. The adentitia is compressed, but otherwise unaffected.

The changes in other organs include enlargement of the heart, edema, and congestion of the lungs, and occasionally degenerative changes in the heart and skeletal muscles. In one case degenerative lesions were found in a nerve ganglion adherent to the aorta. It was thought that these changes might have some etiologic relation to the vascular lesion, but a thorough study of all our material failed to reveal lesions in other animals or in other ganglion of the same animal. The affected ganglion was in the adventitial tissue of an aneurysmal dilation, and the effects of pressure and disturbed blood supply were sufficient, apparently, to account for the changes observed.

The Mode of Action of Adrenalin. The manner in which adrenalin produces these lesions is a matter of widely varying opinion, and, unfortunately, one which cannot readily be determined by our method of experimentation. Until we know more about the toxic action of adrenalin and can distinguish between the lesions due to this action and those due to increased blood pressure, and especially between its direct and secondary effect on the blood-vessels, we can hope for no elucidation of this problem. Drummond,[9] who has recently made a thorough study of the histologic lesions caused by adrenalin, divides all into those due to toxic action and those due to increased blood pressure. It is obvious that such a classification is difficult, for it is impossible to determine to what extent degenerative lesions are due to interference with the circulation through action on the blood vessels.

A discussion of the variety of ways in which adrenalin might act, directly or indirectly, to cause degenerative changes in the media of the aorta would, in the present state of our knowledge, be of little value. The difficulty of reaching definite conclusions is illustrated by the diversity of opinion expressed by those who have previously produced the lesions here described. Josué believes them to be due to a combination of a specific toxic influence and the increased blood pressure. Rzentkowski believes in the latter influence only. Erb ascribes an important influence to disturbance of the vasa vasorum. Fisher thinks that, aside from the increased blood pressure, disturbances of metabolism play an important part. Lissauer[10] believes that the toxic influence is the most important factor, but offers no explanation of its mode of action.

No definite conclusion can be drawn from our own experiments. The observation that the earliest changes occur in the media and are apparently primary in the smooth muscle fibres suggests, in view of the well-known physiologic action of adrenalin on this tissue, a direct and selective toxic action; but the absence of similar lesions in vessels other than the aorta does not support this view. For the same reason, and also because of the absence of changes in the adventitia, the vasa vasorum theory appears to be untenable. On the other hand, if we assume, as is very probable, that the changes in form and arrangement of the elastic fibres are due to the same factor or factors which causes the destruction of the muscle cells, and are not secondary to the latter, we have a strong argument in favor of the influence of a greatly-heightened blood pressure at the time of the ischaemia due to the primary action of the adrenalin. In other words it is possible that at the period of vascular spasm produced by the adrenalin the nutrition of the vessel wall is altered. This would not explain the limitation of the lesion to the aorta but the added mechanical disturbance due to the extreme distention of the vessel wall would appear to be sufficient to bring about a condition analogous to anaemic necrosis. These problems, however, must be settled by other methods of experimentation. Although it is impossible to determine to what extent the primary changes are mechanical and to what extent toxic in nature, it is certain that some of the secondary changes, as the fracture of elastic fibres and the formation of aneurysms, are largely due to mechanical factors.

Comparison of the Experimental Lesions and those Occurring in Man. If due allowance is made for the difference in size between the aorta of the rabbit and that of man it must be admitted that the lesions produced in the former as the result of the administration of adrenalin are somewhat similar to those occurring in human arteriosclerosis. They are not, however, analogous. All the essential processes are represented, and, considering the delicate character of the wall of the rabbit's aorta, the lesions are relatively as extensive and cause the same degree of deformity. There is, however, as compared with the human lesion, a difference in the initial lesion and in the degree of atheroma which is insignificant, and limited to the media. Extensive atheroma, however, cannot be expected in a vessel wall as thin as the rabbit's aorta; and, moreover, in none of these experiments has a period of time sufficient for the occurrence of degeneration in areas of excessive intimal proliferation elapsed. More prolonged experiments will yield, it is to be hoped, lesions more conclusive in this respect. For the present the condition may perhaps be regarded as arteriosclerosis for the rabbit, but not as a condition analogous to the arteriosclerosis of man.

In the light of the information gained from the study of these experimental lesions it would be desirable, perhaps, to critically discuss the various theories concerning the nature of arteriosclerosis, and especially the character and sequence of the histologic changes. Such discussion, however, does not come within the scope of this communication, and many minor points must be determined before comparisons are justifiable. It is sufficient for the present to point out the strong support afforded Thoma's view that the primary lesion of arteriosclerosis occurs in the media, and is, essentially, the result of injury to the elastica and that the changes in the intima constitute a repair process, the object of which is to compensate for the weakened media and the widened lumen.

EXPLANATION OF PLATES I AND II.

Fig. 1. Gross appearance of a portion of the aorta from an animal which had received 27 injections and was killed on the 29th day. The drawing is twice the actual size of the original specimen.

Fig. 2. Diffuse degeneration of central zone of media; 11 injections; 24th day; haematoxylin and eosin; 4 oc., 3 obj.—Leitz.

Fig. 3. Microscopic picture of lesion shown in fig. 1. Destruction of media with infiltration of lime salts; extensive proliferation of intima and subintimal tissue; haematoxylin and eosin; 4 oc., 3 obj.—Leitz.

Fig. 4. Elastic tissue stain of an area very similar to the above illustrating extreme destruction of the elastica.

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To illustrate Drs. Pearce and Stanton's article on "Experimental Arteriosclerosis"

Albany Medical Annals, February, 1906

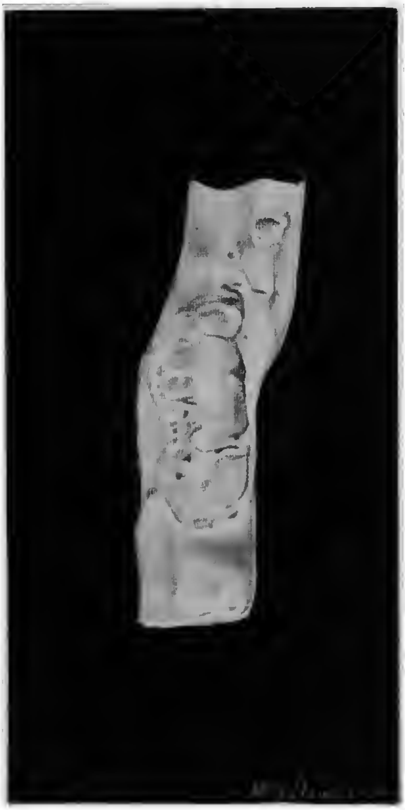

FIG. 1

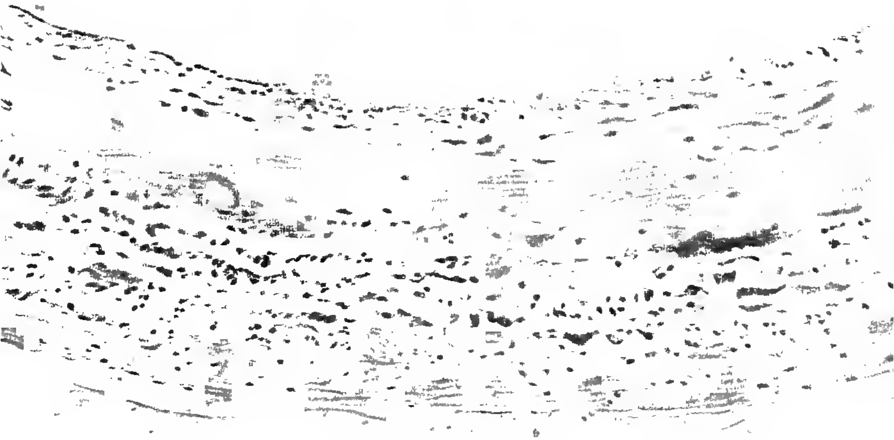

FIG. 2

PLATE I

To illustrate Drs. Pearce and Stanton's article on "Experimental Arteriosclerosis"

Albany Medical Annals, February, 1906

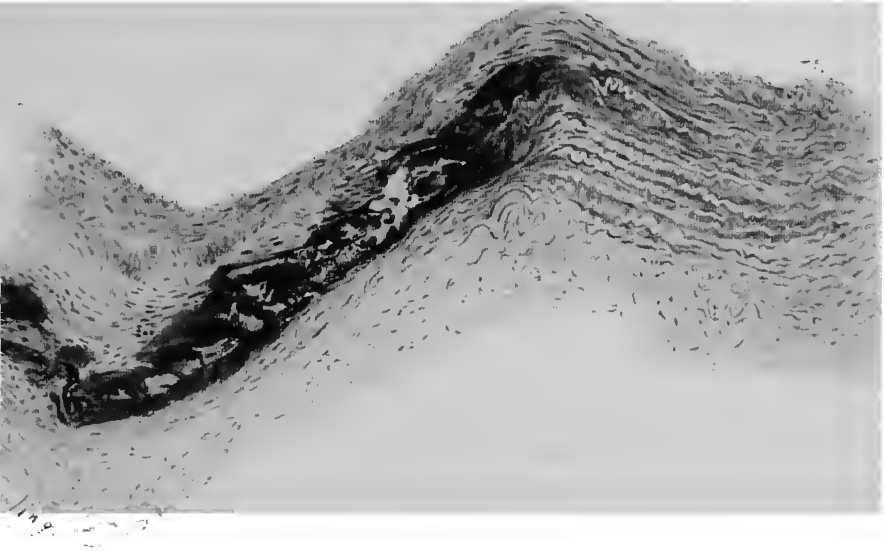

FIG. 3

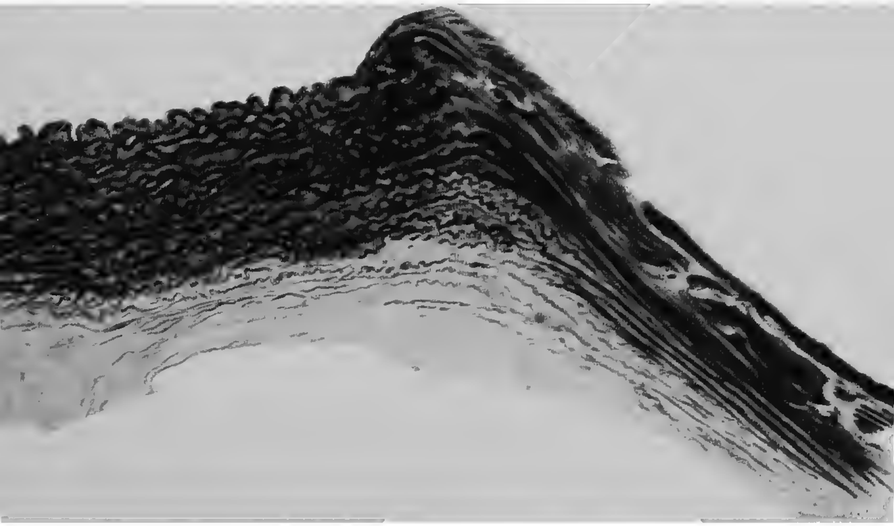

FIG. 4

PLATE II

Reprinted from ALBANY MEDICAL ANNALS, December, 1905.

THE SEQUENCE OF THE PATHOLOGIC CHANGES IN APPENDICITIS.*

A STUDY OF THE SIGNIFICANCE OF THE LESIONS FOUND IN DIFFERENT STAGES OF APPENDICITIS, BASED ON THE PATHOLOGIC FINDINGS IN A SERIES OF OPERATIVE CASES

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Within recent years much has been written concerning the pathology of appendicitis. The anatomic characteristics of the different varieties of appendicitis, together with the secondary lesions accompanying the primary appendiceal inflammation, have been most carefully described and abundant statistics dealing with the relative frequency of the different types of appendiceal and periappendiceal lesions exist. In spite of all this accumulated knowledge, the subject of the pathology of appendicitis is not by any means a closed chapter, but continues to be prominent in medical discussions and literature. The reason for this, perhaps, may lie in the fact that it has not yet been generally recognized that the different pathologic conditions, as they are encountered at operation in cases of appendicitis, represent, for the most part, simply different stages of an inflammatory process involving primarily the appendix and accompanied, in a large proportion of cases, by a more or less extensive secondary involvement of the peritoneal cavity. Most of the studies dealing with the description and classification of the different pathologic varieties of appendicitis are based on a study of the lesions without reference to the duration of the symptoms previous to the observation of the pathologic condition and for this reason such studies throw little light on the pathologic history of the disease.

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A study of the pathologic history of appendicitis resolves itself into a study of the processes of inflammation and repair as they occur in this disease, and a knowledge concerning the progress of these processes can best be obtained by a combined clinical and pathologic study of a sufficiently large series of cases, tabulating the pathologic findings according to the time which has elapsed between the onset of the attack and the observation of the pathologic condition. When the lesions are studied in this way, there is found to exist a striking general uniformity of the microscopic appearances at each of the succeeding periods following the onset of symptoms. This uniformity in the microscopic appearances exists in spite of decided variations in the gross appearances of the appendices, and the fact that the microscopic features prominent at one period may be either increased or diminished in preceding or in subsequent stages, shows that we have to do with a continuous process and that it is probable that the majority of cases presenting the characteristic lesions of patients operated on on the tenth day would, seven days earlier, have presented the lesions characteristic of the third day. The results of such studies, therefore, should serve not only as a basis for a knowledge of the pathologic history of the disease, but should aid also in the diagnosis of the probable lesions existing at any given period during the attack.

OBSERVATIONS OF CASES.

The following observations are based on a study of the condition of the peritoneum as found at operation in 485 cases of appendicitis[1] occurring at the Albany Hospital during the past six years, and of the condition of the appendix in 188 of these cases, the descriptions and sections of which are on file in the Bender Laboratory. The pathologic findings in this series of cases were studied with special reference to the relations existing between the character of the lesions and the stage of the disease.

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[1] The data referring to the condition of the peritoneum is taken from the notes made at the time of operation: all else is based on the descriptions and sections on file in the Bender Laboratory. The histologic observations have necessarily been confined to those cases, the sections of which have been preserved and are available for present study. While the anatomic variations, especially as regards the condition of the peritoneum, are so variable as to require a large series of cases on which to base satisfactory observations, this is not the case with the histologic changes which are so uniform that it is not deemed necessary to include a larger series of cases.

In summarizing the results of the observations in this series of cases, those cases operated on during the first, second, third, fourth, fifth and sixth days of the attack are considered in separate groups for each day. Those cases operated on from the seventh to the tenth, from the eleventh to the fifteenth and from the sixteenth to the thirtieth day are considered in three corresponding groups; while all cases operated on one month or more after the occurrence of a definite attack are considered as a separate group.

The following is a summary of the more striking features of the pathologic process:[2]

First Day Group.—This was made up of ten patients operated on during the first twenty-four hours following the onset of symptoms. In two cases (20 per cent.) there was a sero-purulent intraperitoneal exudate without perforation of the appendix. In one other case, the omentum was adherent by a fibrinous exudate to a gangrenous appendix. The gross appearances of the nine appendices studied histologically varied greatly. Two showed plainly visible gangrenous areas, one was described as normal, while in others the only macroscopic evidence of disease was a congestion or slight opacity of the peritoneum, with a swollen or hemorrhagic mucosa.

In sharp contrast to the often apparently insignificant gross lesions is the microscopic picture, which is essentially similar in all cases and consists of an intense, diffuse, polynuclear leucocytic infiltration with focal areas of hemorrhage and necrosis involving all coats with a more or less extensive destruction of the mucosa and, in many cases, a fibrinous or fibrino-hemorrhagic exudate on the peritoneal surface. One of the most striking features in these cases is the presence throughout the majority of the sections of numerous areas of necrosis. These areas are larger, but are not more numerous in those cases which show macroscopic evidences of gangrene.

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[2] The accompanying charts show graphically the relative frequency of the various types of lesions grouped according to the different periods as enumerated above and also serve to give an idea of the relationships existing between the character of the pathologic lesions and the duration of the disease. The absence of irregular fluctuations in the platted curves is evidence that the series of cases here studied has been sufficiently large for the purposes of this investigation, although the relative heights of the different curves must vary somewhat in different series of cases.

Second Day Group.—This was made up of twenty-three patients operated on during the second twenty-four hours following the onset of symptoms. In eight (34.8 per cent.) of the cases of this group intraperitoneal fluid exudates, usually of considerable extent and of a sero-purulent or purulent character were present. As in the first-day cases, the appendices in this group which were studied histologically, presented no uniformity as to gross appearances. Some of them are described as "gangrenous," others as "catarrhal" and "ulcerative" or "slight periappendicitis."

Microscopically, all the appendices show an intense leucocytic infiltration involving all coats, together with a more or less extensive ulceration of the mucosa, while 70 per cent. show a well-marked fibrinous or fibrino-purulent exudate on the peritoneal surface. In those cases which presented macroscopic evidence of gangrene the areas of necrosis as seen microscopically are decidedly more extensive than in the similar cases of the first-day group, while in those cases which did not present macroscopic evidences of gangrene the focal areas of necrosis so prominent in the first-day cases are still evident in the majority of sections, but are often obscured by the leucocytic infiltration.

Third Day Group.—This was made up of fifty-three patients operated on during the third day following the onset of symptoms. Twenty-nine (53.7 per cent.) of the cases in this group were characterized by intraperitoneal fluid exudates which were of a distinctly purulent character and usually described as periappendiceal abscesses. The macroscopic evidences of disease were distinctly more prominent than in the earlier cases. Forty per cent. of the appendices studied histologically were described as "gangrenous" and all but three of the others as "acute" or "acute ulcerative."

Microscopically, two recurrent cases show decided chronic changes, but no evidence of an acute process. The remaining cases all show a diffuse inflammation like that seen in the earlier groups. In the macroscopically gangrenous cases the necrosis is prominent, while in the non-gangrenous cases focal areas of necrosis are seen only in the mucosa. The most striking histologic feature which distinguishes this group from the earlier groups is the evidence of beginning repair as seen by the presence of fibroblasts in all sections. These new-formed connective tissue cells are especially numerous in the region of the peritoneum, although present in other areas, particularly in those cases showing the least marked leucocytic infiltration.

Fourth Day Group.—This was made up of thirty-one patients operated on during the fourth day following the onset of symptoms. In seventeen (54.5 per cent.) of the cases in this group purulent periappendiceal exudates usually described as abscesses were present. With the exception of one normal and one chronic atrophic appendix (microscopic diagnosis), all of the appendices in this group presented well-marked anatomic changes in general similar to those seen in the third-day cases.

Microscopically, the gangrenous cases show large areas of complete necrosis, the histologic picture differing but little from that seen in the gangrenous cases of the third-day group. In sections of the non-gangrenous cases, and in sections taken at some distance from the necrotic areas in the gangrenous appendices, the most noticeable histologic feature which distinguishes this group from the preceding one is a decided increase in the relative number of fibroblasts and the presence of numerous lymphocytes and, in several cases, plasma cells. In those cases accompanied by a periappendiceal exudate a few fibroblasts and many new-formed blood vessels can be seen extending into the exudate from the peritoneal surface. Focal areas of hemorrhage into the exudate occurring from these new-formed blood vessels are seen in many of the sections.

Fifth Day Group.—This was made up of twenty-seven patients operated on during the fifth day following the onset of symptoms. In fifteen (55.5 per cent.) of the cases of this group periappendiceal suppuration was noted. With the exception of one recurrent case, all of the appendices presented easily recognizable anatomic changes most evident in the mucosa or on the peritoneal surface.

Microscopically, the lesions may be divided into two rather sharply defined groups. In the cases presenting macroscopic evidence of gangrene, the necrosis and polynuclear leucocytic infiltration is the predominating characteristic, although the repair process is well advanced in several instances. In the non-gangrenous cases the polynuclear leucocytes have practically disappeared except at the surfaces of the ulcerations in the mucosa and of the periappendiceal exudates. Throughout the coats of the appendix there is a marked increase in the number of fibroblasts and often an intense lymphocytic infiltration. In the periappendiceal exudates the new-formed blood vessels penetrate to a greater distance than in the fourth-day group and this granulation tissue is decidedly richer in fibroblasts.

Sixth Day Group.—This was made up of twenty-four patients operated on during the sixth day following the onset of symptoms. Twelve (50 per cent.) of the cases in this group showed evidence of periappendiceal suppuration and all the appendices showed well-marked anatomic changes. The partially organized periappendiceal exudates were very noticeable in those cases accompanied by abscess formation.

Histologically, the repair processes are decidedly more advanced than in the fifth-day group. The gangrenous cases show well-marked evidences of repair, the histologic picture of which is similar to that seen in the non-gangrenous cases of the preceding group. A number of these cases, however, present the picture of a fresh acute process engrafted on the subacute process, there being a diffuse leucocytic infiltration with areas of hemorrhage and necrosis, the latter often involving areas rich in fibroblasts. The non-gangrenous cases now show areas in which the fibroblasts are massed together and elongated so as to resemble young connective tissue cells. Small ulcers in the mucosa have apparently been largely repaired.

Seventh to Tenth Day Group.—This was made up of one hundred and six patients operated on from the seventh to the tenth day of the attack. Fifty (47.1 per cent.) of the patients operated on during this period had also periappendiceal suppuration, which in all but six cases was more or less localized and usually accompanied by marked evidences of organization. Anatomic changes, for the most part, were well marked, particularly so in those cases characterized by partially organized periappendiceal exudates. In the cases unaccompanied by periappendiceal exudates the anatomic lesions were decidedly less prominent than in the earlier groups, and four of the appendices studied histologically were described anatomically as cases of catarrhal appendicitis.

Histologically, the repair process has become still more advanced, so that in 18 per cent. of the appendices in this group the organization is so far advanced as to present the picture of a distinctly chronic process, the evidence of a previous active inflammation being shown by the presence of new-formed fibrous tissue which is rich in connective tissue cells. In addition to the new-formed connective tissue in these cases, numerous focal collections of lymphocytes are seen, which are most noticeable in the subperitoneal tissues and muscular coats. In 64 per cent. of the appendices in this group the presence of the fibroblasts and other evidences of active repair is noticeable, being most marked in those cases showing partially organized periappendiceal abscesses. Eighteen per cent. of the cases show evidences of an acute process, which is seen as a diffuse polynuclear leucocytic infiltration, often accompanied by hemorrhage and necrosis. In all but one of these acute cases, however, there are also evidences of an older subacute process.

Eleventh to Fifteenth Day Group.—This was made up of forty-eight patients operated on from the eleventh to the fifteenth day following the onset of symptoms. In this group in but sixteen cases (33.3 per cent.) were periappendiceal abscesses found, and when present the pus usually occurred in small collections surrounded by thick masses of new-formed connective tissue. The macroscopic appearances of the appendices in this group varied greatly: Two were described as "gangrenous," two as "acute," three as "normal," and the rest as "subacute," "chronic," "chronic obliterative," "chronic periappendicitis" and "catarrhal." Except in those cases showing an acute process and in those accompanied by evidences of periappendiceal organization, the gross changes in the appendices, as a rule, were not prominent.

Microscopically, 68 per cent. of the appendices present lesions of a typically chronic character, the most constant feature of which is an increase of connective tissue, usually well marked and accompanied by conspicuous focal collections of lymphocytes; the latter occur, as a rule, within the perivascular and interstitial lymph channels of the peritoneal and muscular coats. An additional 10 per cent. show a less advanced stage of repair corresponding to the predominating lesion in the preceding group. Ten per cent. show changes confined to the mucosa, such as are usually described as catarrhal appendicitis. Ten per cent. show the presence of acute inflammation, in addition to subacute or chronic changes.

Sixteenth to Thirtieth Day Group.—This was made up of forty-six patients operated on from the sixteenth to the thirtieth day following the onset of symptoms. Abscesses were present in 19 per cent. of the patients operated on at this period of the disease; this decrease in the frequency of pus being accompanied by a corresponding increase in the number of cases showing adhesions without the presence of pus. In the cases in which there was no histologic evidence of an acute or subacute inflammatory process, the macroscopic changes in the appendices were not prominent except in those cases showing an obliteration of the lumen or evidences of periappendiceal organization.

Microscopically, 69 per cent. of the cases show only chronic changes. In these the new-formed connective tissue is more fibrous than in the similar cases of the preceding group, while the focal collections of lymphocytes, so prominent in the preceding group, are now less numerous. A few cases still show acute or subacute lesions, in addition to more chronic changes. Ten per cent. of the cases must be considered as examples of catarrhal appendicitis, as the demonstrable pathologic changes are confined entirely to the mucosa.

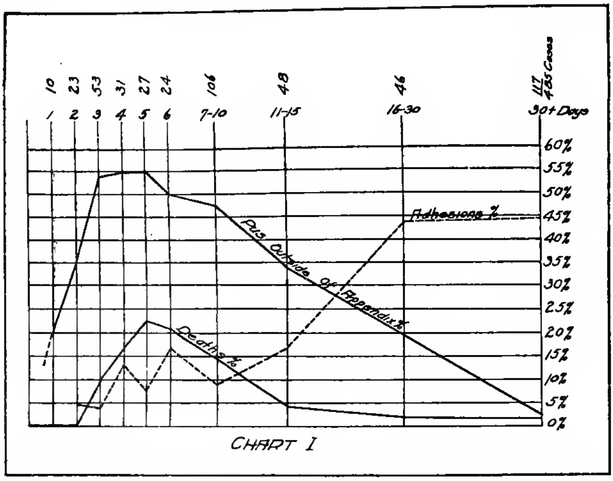

Chart 1.—Condition of the peritoneum and death rate. The term "pus outside of appendix" is used to include all cases accompanied by purulent intraperitoneal fluid exudates, either localized or general. The term "adhesions" is limited to those cases presenting organized adhesions without the presence of pus.

Patients Operated on One Month or More After a Well-defined Attack.—In this group are included one hundred and seventeen patients, having, for the most part, histories of long-standing chronic, recurrent or relapsing appendicitis. In three cases (2.5 per cent.) small foci of pus were found in connection with extensive adhesions. In 44 per cent. of the cases there were well-marked adhesions, without the presence of pus. With the exception of the cases of chronic obliterative appendicitis, the macroscopic changes in the appendices were usually not prominent, and many of the cases which show an extensive increase of interstitial connective tissue were described as macroscopically normal.

No appendices in this group show microscopic evidence of an acute or subacute inflammatory process. Six per cent. of the appendices are microscopically normal; 16 per cent. are examples of catarrhal appendicitis; 52 per cent. are microscopically examples of more or less well-defined chronic interstitial appendicitis; 26 per cent. are examples of chronic obliterative appendicitis.

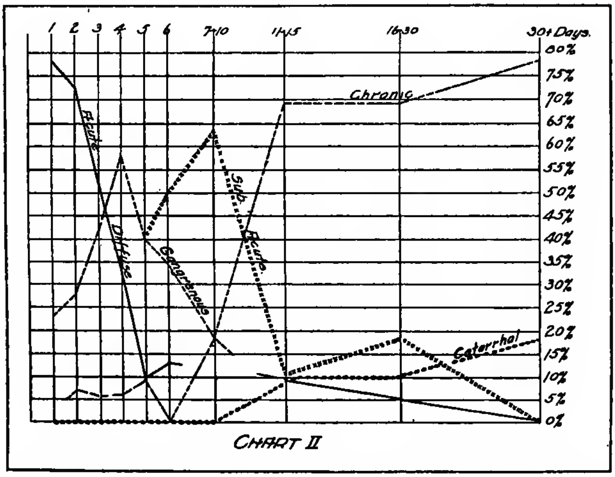

Chart 2—Histologic condition of appendix. The term "acute diffuse" is used to include all appendices showing a diffuse polynuclear leucocytic infiltration without the presence of macroscopic evidences of gangrene. Under the term "gangrenous" are included all appendices showing macroscopic areas of gangrene with or without perforation. Under the term "subacute" are included all appendices showing evidences of active repair unaccompanied by a polynuclear leucocytic infiltration. Under the term "chronic" are included all appendices showing a distinct increase of connective tissue without evidences of active repair or leucocytic infiltration. All appendices showing changes confined to the mucosa are included under the term "catarrhal."

SUMMARY.

The character of the histologic changes is essentially similar in all of the appendices of this series which were removed during the first few days of the disease and is that of a severe, diffuse inflammation, accompanied by focal areas of hemorrhage and necrosis. These focal areas of necrosis may increase in extent during the first few days and give rise to macroscopic areas of gangrene or they may remain of microscopic size and be quickly repaired. The various anatomic varieties, such as the gangrenous, perforative and ulcerative forms, are determined by the extent and distribution of these necroses.[3]

Evidences of repair are seen as early as the third day, and in the non-gangrenous cases the histologic picture of an acute process has changed to that of a distinctly reparative process by the fifth day. In those cases in which the necrosis is so extensive as to give macroscopic evidences of gangrene, the histologic picture of an acute process persists for a longer period, but even in these cases (unless there is a later acute process engrafted on the earlier lesion) the evidences of repair are by the sixth or seventh day the predominating feature of the lesion. Evidences of a recurrent acute process are by no means uncommon, and were present in from 10 to 15 per cent. of all cases after the first week.

During the second week of the attack the repair proceeds rapidly. Fibroblasts, new-formed blood vessels and lymphocytes making up the chief features of the histologic picture. The rapidity with which the repair of the appendix itself is accomplished depends chiefly on the extent of the primary destruction and on the presence or absence of a periappendiceal exudate. By the end of the second week, in the majority of cases, the repair is so far advanced that the new-formed connective tissue may constitute the only evidence of a previous inflammation, although in cases with extensive periappendiceal exudates evidences of active organization of the exudate itself are still to be seen.

Except for the completion of the repair in those cases accompanied by more extensive periappendiceal lesions, the histologic changes occurring after the second week are seen chiefly in the more fibrous nature of the new-formed connective tissue which persists so as to be readily recognizable in the majority of cases. Of the patients operated on one month or more following an acute attack, 78 per cent. were cases of chronic interstitial or chronic obliterative appendicitis very often accompanied by adhesions. Six per cent. of the appendices were apparently normal, while in 16 per cent. the demonstrable pathologic changes were confined to the mucosa.

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[3] In connection with the well-known difficulties encountered in attempting to predict the subsequent course of a case of appendicitis seen during the first few days of the disease, it is a fact worthy of emphasis that the early histologic changes were essentially similar, irrespective of the severity of the clinical symptoms, in all the cases observed; and that the later more important gross changes, such as gangrene and perforation, were dependent on the apparently more or less accidental factors which determined the extent and distribution of the necrosis.

A notable feature seen in the histologic examination of these cases is the fact that in no instance was the pathologic change confined to the mucosa in the appendices examined during the first ten days of the attack.

In this series of cases, purulent fluid outside of the appendix was present in 51 per cent. of the patients operated on from the third to the tenth day of the attack.[4] After the tenth day the relative number of cases accompanied by abscesses decreases steadily, while on the other hand occurs corresponding rise in the number of cases presenting adhesions without the presence of pus, which would seem to indicate that resolution by absorption had played an important rôle in the repair of this lesion. This is doubtful, however, and is probably in large measure due to the fact that the involvement of the peritoneal cavity was less extensive in those cases in which operation was delayed. In a number of cases, however, the adhesions were so massive as to leave little doubt of the previous presence of an extensive periappendiceal exudate.

After the third day the exudates on the peritoneal surface contain highly vascular granulation tissue, and it is probable that the high operative death rate between the third and tenth days in part may be accounted for by absorption from the denuded granulating surfaces as well as by the extent of the peritonitis and the bad general condition of the patients.

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[4] This includes the cases of general peritonitis as well as those accompanied by a more localized periappendiceal exudate. According to the reports of the operations, the cases of general peritonitis were distributed as follows:

First day	No case.
Second day	One case with recovery.
Third day	Seven cases with five deaths.
Fourth day	Four cases with four deaths.
Fifth day	Six cases with five deaths.
Sixth day	Four cases with four deaths.
Seventh to tenth day	Six cases with six deaths.
Eleventh to fourteenth day	One fatal case.

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PRIMARY CARCINOMA OF THE VERMIFORM APPENDIX, WITH A REPORT OF THREE CASES.

Read before the Medical Society of the County of Albany, November 8, 1905.

BY LEON K. BALDAUF, M. D.

(From The Bender Laboratory, Albany, N. Y.)

The recognition of primary carinoma as a not infrequent disease of the appendix has been brought about during the past ten years as the direct result of the increasing tendency to examine microscopically all tissues removed by the surgeon. Casuistic reports of instances of this disease, thus brought to light, have appeared in rapid succession since 1896. Letulle and Weinberg, Harte and Willson, A. O. J. Kelly, Elting and Moschowitz have each reported small groups of cases observed in comparatively short periods of time. Their communications containing, as they do, general conclusions drawn from a critical review of the literature, have done much to bring the important facts concerning primary carinoma of the appendix to the general attention of the profession. Nevertheless from a perusal of this literature it is evident that many points are still in doubt and that final general conclusions can be reached only after a much larger number of cases have been placed on record.

It is with the desire therefore to add to the material already available, and not necessarily to present anything new, that this communication comprising a report of three cases and a brief summary of those already described is presented.

Case I—Records of the Bender Laboratory, Surg. Path. No. 04:128.

Clinical History—Mr. H., male, aged thirty-eight, was admitted to the Albany Hospital on February 22, 1904: service of Dr. Albert Vander Veer.

Family history—Negative. *Past history*—Typhoid fever at fourteen; otherwise negative. *Present illness*—On Sunday, February 21st, the patient experienced sharp pains radiating from the center of the abdomen to the right iliac fossa; several attacks of vomiting; no constipation. Blood count showed a leucocytosis of 19,000. *Clinical Diagnosis*—Acute appendicitis.

Operation, February 22, 1904—"Appendix bound down by adhesions and underneath umbilicus. Beginning peritonitis. Appendix easily removed." Recovery uneventful. Discharged March 9, 1904.

Pathological Examination—The specimen consists of the distal portion of the appendix, which is five centimeters in length. The meso-appendix is considerably thickened. The peritoneal surface is covered with greyish yellow fibrin. The lumen is patent throughout. The mucosa, which in general, is of an opaque yellowish color, and deeply injected, exhibits a few small foci of necrosis. *Anatomical Diagnosis*—Acute appendicitis.

Microscopic Description—The lumen is much smaller than normal and contains desquamated epithelial cells, leucocytes and granular debris. The mucosa, slightly infiltrated with leucocytes, is intact in about two-thirds of its circumference, but has entirely disappeared at that portion of the organ to which the mesentery is attached. Here is a slightly irregular ulcerated surface. The tissue beneath this ulcer is composed of closely arranged connective tissue forming small alveoli, in which are masses of epithelial cells. This new growth replaces entirely the mucosa at this point and invades the muscular coat. The masses of cells are of small size near the base of the ulcer, but increase in size as the muscularis is reached; though in the outer portions of the latter they again diminish in size and are not very abundant. Beneath the peritoneum are found numerous nests of epithelial cells larger than those seen in any other portion of the appendix. These pass for a short distance into the loose fatty tissue of the meso-appendix, extending apparently along the lymphatics. The cells composing the epithelial masses are oval or polygonal in shape with considerable light protoplasm and vesicular nuclei. No tendency to tubular arrangement is evident. The stroma is a loose connective tissue with numerous lymphoid and plasma cells.

Except at the mesenteric attachment the serosa is obscured by a mass of young granulation tissue diffusely infiltrated with leucocytes and containing small areas of haemorrhage.

Microscopic Diagnosis—Carcinoma simplex of the appendix with ulceration. Acute appendicitis; periappendicular suppuration.

Case II—Records of the Bender Laboratory, Surg. Path. No. 04:200.

Clinical History—Mr. B., aged twenty-three, was admitted to the Albany Hospital on March 15, 1904; service of Dr. W. G. MacDonald. *Family history*—Negative. *Previous history*—Negative. *Present illness*—Patient thinks it began in September, 1903, when he had severe pains in right iliac region lasting for a week. He had a similar but more severe attach in October. Present attack began on evening of March 13th, with pain in right lower quadrant of abdomen. Pain of varying severity has continued since. *Clinical Diagnosis*—Subacute appendicitis.

Operation, March 18th—"Appendix removed with difficulty."

Pathological Examination—Specimen consists of appendix and a piece of blood stained fatty tissue. The appendix considerably thickened measures seven centimeters in length and eight-tenths of a centimeter in greatest diameter. The serosa is covered with tags of fairly firm fibrous tissue. The mucosa is swollen and granular, while the lumen is completely obliterated at a point five centimeters from the distal end. The fat tissue accompanying appendix is haemorrhagic and firmer than usual.

Anatomical Diagnosis—Chronic appendicitis and periappendicitis.

Microscopic Description—The lumen of the appendix is entirely obliterated, and mucosa and submucosa are replaced by a new growth of loose connective tissue, in the meshes of which are epithelial cells closely massed. This new growth penetrates to a slight extent the muscular coat, and at only one point, opposite the attachment of the meso-appendix, the masses of epithelial cells reach the subserous tissues. Here however the invasion is sharply limited, and no extension to the meso-appendix is apparent. The muscular and subserous coats show evidence of a slight chronic inflammation, but it is impossible to say whether the obliteration of the lumen preceded or was the result of the new growth. Although serial sections have been made at various levels of the tumor, it has been impossible to determine definitely this question. Above the level of the tumor the organ shows evidence of a mild chronic inflammation, but is otherwise negative.

Microscopic Diagnosis—Carcinoma simplex of appendix with obliteration of lumen. Chronic appendicitis.

Case III—Records of the Bender Laboratory, Surg. Path. No. 04:406.

Clinical History—Miss A., aged eight years, admitted to the Albany Hospital on May 14, 1904, service of Dr. Edgar A. Vander Veer. Nothing of interest in family or previous history. There were no symptoms referable to the appendix until May 14th, when a severe acute attack of appendicitis developed. At the operation, on May 16th, the appendix was found to be surrounded by an inflammatory mass, which was adherent also to the omentum. In the manipulations attending the removal of this mass, it ruptured and a small amount of pus escaped.

Pathological Examination—Specimen consists of appendix measuring five and five-tenths centimeters in length, the upper half of which averaging five millimeters in diameter, is practically normal. The lower half is buried in a mass of partially organized tissue which surrounds the tip of the appendix in a layer approximately five millimeters in thickness. The wall of this portion of the appendix is thickened and indurated. The mucosa is injected, and at one point shows a superficial loss of substance. Lumen normal. Accompanying the specimen is a piece of omentum measuring 4 x 3 x 1.5 centimeters, showing a core of soft yellowish material surrounded by a zone of translucent granulation tissue.

Anatomical Diagnosis—Partial organization of periappendicular abscess.

Microscopic Description—The organ is entirely surrounded by a mass of granulation tissue, which in some places is quite fibrous while in other places it is very loose and vascular. Leucocytes are abundant throughout, and here and there are grouped in distinct foci. The meso-appendix is extensively involved. The appendix, greatly distorted, is found a little to one side of the center of this mass. The lumen is compressed, triangular in shape, and contains a few leucocytes and a small amount of granulate material. A very definite mucosa is seen, but the glands are few in number and irregularly arranged. The cylindrical surface epithelium of the mucosa is very distinct and show a superficial ulceration over an area corresponding to a new growth which involves the submucosa. Here the mucosa contains but few glands and several small irregular masses of epithelial cells separated by a loose stroma rich in lymphoid and plasma cells. This new growth involves the entire submucosa, in which the masses of epithelial cells are larger and the stroma more fibrous. There is no invasion of the muscular coat.

Microscopic Diagnosis—Carcinoma simplex with ulceration; periappendicular abscess.

With the exception of Case III, which is the first reported instance of cancer of the appendix occurring in the first decade of life, these cases add little that is new to our knowledge of cancer of this organ. They however increase the number of reported cases available for comparison and as the total is now 34, if we include the three here reported, a brief resumé of the subject may be justifiable.

SUMMARY OF REPORTED CASES OF PRIMARY CANCER OF THE APPENDIX.

In the following paragraphs is given a brief summary of each of the cases* of primary cancer of the appendix reported prevous to 1905. The first twenty are those examined and accepted by Elting in 1903. To these, others since reported have been added and although the list may not be completed, it represents the result of a very thorough search of the literature. No case has been included unless the diagnosis was confirmed by microscopic examination.

1. *Beger* (1882). Male, aged forty-seven. Three and one half years before final operation a tumor of right inguinal region was incised; a litre of pus was removed; sinus persisted. Adenocarcinoma of appendix involving caecum by extension; metastases in retroperitoneal lymph nodes. Died thirty-six hours after operation.

2. *Stimson* (1896). Female, aged forty-four. Severe attack of appendicitis ten years previously. Two mild attacks within two months before operation. "Degenerated carcinoma."

3. *Letulle and Weinburg* (1897). Autopsy on individual dying of tuberculosis. Starting point of carcinoma at line of fusion in appendix, the lumen of which had been obliterated by preexisting chronic inflammation.

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*Since preparing this list Kelly and Hurdon have reported three additional cases. See Kelly and Hurdon, The Vermiform Appendix and its Diseases, W. B. Saunders and Co., Philadelphia and London, 1905.

4. *Letulle and Weinburg* (1897). Terminal extremity of appendix seat of a peculiar adenomatous hyperthrophy associated with obliterative appendicitis. The carcinoma had begun in scar and had involved all the coats of the appendix.

5. *Mosse and Daunic* (1897). Female, aged fifty. Autopsy. No history of appendicitis. Tumor in mucosa and muscularis in part alveolar and in part cylindrical cell in type.

6. *Wright* (1898). Autopsy. No history. Adeno-carcinoma at base of appendix. Peritonitis due to perforation of appendix.

7. *Hurdon* (1900). Female, aged twenty-four. Pain in lower part of abdomen and back since first child birth, associated latterly with constant aching in right lumbar region. Operation for retroflexed uterus; appendix involved in dense adhesions. Adeno-carcinoma involving all coats of appendix.

8. *Giscard* (1900). Male, aged thirty-seven. Two severe attacks of appendicitis within nine months. Operation; abscess about appendix; adeno-carcinoma.

9. *Rolleston* (1900). Female, aged twenty-six. Four attacks of appendicitis within fifteen months. "Spheroidal-cell carcinoma near tip." In poor health several months after operation.

10. *Letulle and Weinburg* (1900). Twelve and a half years of age. "Muco-membraneous colic" since infancy; history of two attacks of appendicitis at intervals of a year. Operation after subsidence of second attack, which was very acute. Appendix adherent to iliac fossa, upper portion dilated, lower portion contracted, contains an enterolith. *Histological examination*—chronic appendicitis with ulceration in upper portion and obliteration and carcinoma in lower portion.

11. *Letulle and Weinburg* (1900). Autopsy. No history. Chronic obliterative appendicitis with cancer at tip of organ.

12. *McBurney* (1901). Female, aged twenty-three. Attack of appendicitis two years before she came under observation. A second attack two months before operation. Strictures at base and tip of appendix; tumor at tip. Carcinoma simplex.

13. *McBurney* (1901). Male, aged thirty. Autopsy. No previous history of appendicitis. Carcinoma simplex.

14. *Goffe* (1901). Female, aged fifteen. For more than a year pain in the appendiceal region on exercising. Chronic appendicitis. Carcinoma simplex.

15. *Harte and Willson* (1902). Female, aged twenty-four. At nineteen appendicitis; in bed four weeks. Free from symptoms for three years. At twenty-three, during period extending over whole winter, experienced pains similar to those three years previous. Symptoms disappeared finally, but reappeared in the summer. Operation—almost complete obliteration of appendix. Scirrhus carcinoma at tip.

16. *Harte and Willson.* Male, aged twenty-five. Eight months prior to the operation had more or less continuous pain in the right iliac fossa. Operation—adhesions; perforation, acute suppurative appendicitis. Carcinoma simplex near tip.

17. *Wier* (1902). No clinical history or pathological description. "Carcinoma." No return after three years.

18. *Jessup* (1902). Female, aged thirty-six. No symptoms of appendicitis; operation for disease of uterine adnexia. Cyst of ovary. Appendix bound down with adhesions and therefore removed. Adeno-carcinoma in middle third.

19. *Kelly, A. O. J.* (1902). No clinical history. Operation—acute ulcerative appendicitis. Carcinoma simplex.

20. *Kelly, A. O. J.* (1902). Male, aged eighteen. Well until eight days prior to admission, when symptoms of acute appendicitis developed. Operation—pus about appendix, acute ulcerative appendicitis. Carcinoma simplex at base.

21. *Elting* (1903). Male, aged eighty-one. Autopsy. No symptoms of appendicitis. Colloid cancer of appendix with perforation. No metastases.

22. *Elting* (1903). Female, aged thirty-six. Patient enjoyed good health until eight years previously, when she had an attack of what was called "peritonitis," from which she made a fairly good recovery. Operation for "pelvic disease." No symptoms of appendicitis. Appendix removed with pelvic organs. Obliteration of lumen of entire appendix with carcinoma simplex of distal end. In good health three years after.

23. *Elting* (1903). Male, age ten. Present illness began in January, 1902, with an attack of acute appendicitis which was associated with the formation of an indurated mass in the right iliac fossa, in which after a short time an abscess formed, which opened internally in the right lower quadrant of the abdomen. The sinus still existed when patient was admitted to the hospital. Patient had lost forty pounds. Operation—new growth involving appendix, caecum, ilium, and portions of colon and jejunum, with metastases in adjacent lymph nodes. Died about two weeks after operation. "Primary colloid carcinoma of the appendix of an adenomatous type."

24. *Moschcowitz* (1903). Male, aged thirty-seven. Disturbance for three years, supposed to be alcoholic gastritis; later symptoms of appendicitis with general peritonitis. Operation—general peritonitis. Appendix surrounded by adhesions and partially gangrenous with tumor at tip size of a bean. Adeno-carcinoma. No recurrence eighteen months after operation.

25. *Moschcowitz.* Female, aged twenty. Typical attack of appendicitis. Operation—acute inflamed appendix; carcinoma simplex one inch from tip.

26. *Moschcowitz.* Female, aged twenty-four. Five months pregnant. Foetal movements felt for two weeks. Present history five days duration. Pain in epigastrium, fever, leucocytosis. Exploratory laparotomy. Appendix adherent to iliac fossa. Chronic appendicitis; medullary carcinoma of distal portion.

27. *Burnam* (1904). Male, aged twenty-five years. For two years patient had recurring attacks of pain in right lower quadrant of abdomen. Operation—acute appendicitis with adeno-carcinoma of distal end of appendix.

28. *Norris* (1904). Female, aged twenty-seven. No history of appendicitis. Operation for retroflexed uterus, pyosalpinx and inguinal hernia. Appendix removed because of reddened and adherent distal end. Obliterative appendicitis with carcinoma simplex at tip.

29. *Neri* (1904). Male, aged twenty-nine. Repeated attacks of appendicitis. Chronic appendicitis with adeno-carcinoma.

30. *Jones and Simmons* (1904). Female, aged twenty-six. Four attacks in twelve years, termed colic. Chronic appendicitis with carcinoma simplex at base of appendix.

31. *Cullingworth and Corner* (1904). Female, aged thirty-one. Had had two attacks of pain in right side. Operation for tumor of right broad ligament. Appendix removed on account of bulbous enlargement at distal end. "Spheroidal cell" carcinoma. No recurrence after three years.

Frequency of occurrence. The older statistics, as quoted by A. O. J. Kelly, indicate that before the days of routine microscopic examination carcinoma of the appendix was but rarely seen. Thus in 40,838 autopsies at the Vienna General Hospital from 1870-1892 carcinoma of the appendix occurred, according to the compilation of Madyl and Nothnagel, but twice. Leichtenstern's series of 770 cases of intestinal carcinoma contains three examples of cancer of the appendix. Kelynack in 1893 could find no record of an undoubted primary cancer of the appendix. In this connection he quotes the records of four London hospitals which gave a total of 15,481 new growths but with no mention of a neoplasm of the appendix. Since that time thirty-one cases nearly all detected only upon microscopic examination have been reported. In 1900 Hurdon found but ten cases in the literature and of these but three were confirmed by microscopic examination. Elting in 1903 brought together forty cases, only twenty of which however he accepted as primary. With the three cases here reported the total number of cancers apparently primary in the appendix and confirmed by a microscopic examination is now thirty-four. Cancer of the appendix is therefore no longer a rarity, but these figures unfortunately give no adequate idea of its frequency in relation to other diseases of the appendix. Few operators make it a rule to have all appendices which they remove examined microscopically. As a rule only those which show to the naked eye some unusual appearance are investigated and thus most of the reported cases have been discovered. Little information concerning the incidence of cancer in a large number of appendices examined microscopically as a matter of routine is available. Practically the only series is that of Kelly, who found primary cancer twice in 706 appendices removed at operation. The three tumors here reported occurred in a series of 201 appendices removed at operation and examined microscopically between August 31, 1903, and September 1, 1904.* Previous to September 1, 1903, 320 appendices removed at operation had been examined at the Bender Laboratory, though not always histologically, and as two of Elting's cases were drawn from this number, we have a total of five primary cancers in a group of 521 examinations in one laboratory and representing practically the operations of one hospital (Albany Hospital) for a period of eight years. Moschcowitz's three cases occurred at the Mount Sinai Hospital within a period of sixteen months in a service averaging yearly 200 to 300 operations for appendicitis; all appendices however were not examined microscopically. Neri reports one cancer occurring in a series of eighty appendices removed in Biondi's clinic. It is obviously impossible to draw definite conclusions from these figures. Of the two properly controlled series, Kelly's indicates that cancer occurs in relation to other diseases of the appendix as 1:353, while our series shows a proportion of 1:67. Estimating the other series of cases in the same way, we have for Elting's group a ratio of 1:160, for Moschcowitz's 1:125, while the total number of specimens examined at Bender Laboratory would yield a proportion 1:104. Although these figures vary considerably, it would nevertheless appear justifiable to conclude that routine histological examination of all appendices removed at operation would demonstrate primary carcinoma to be present in about one per cent of all cases.

ETIOLOGY.

The only factors worthy of consideration in this connection are sex, age and antecedent pathological conditions of the appendix.

Sex. An analysis of the twenty-seven cases in which the sex of the patient is stated shows that fifteen were females and twelve males. These figures would indicate that sex is not a predisposing factor, as might appear to be the case from some of the earlier reports which show that three-fourths of the cases occur in females.

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*Dr. Pearce tells me that in the following nine months, ending July 1, 1905, 214 appendices were examined at the Bender Laboratory and that but one primary cancer was found.

Age. One is accustomed to regard carcinoma as a disease of those in or past the fourth decade of life. Carcinoma of the appendix is a surprising exception to this view. Of the twenty-eight cases in which the age is stated, it is seen that all but four of the individuals were under forty years of age and seventeen, or 60.7 per cent., were under thirty.

The largest number of cases in any one decade occurred in the third; the extremes are represented by individuals aged eight and eighty-one years respectively. The first decade is represented by one, the second by five, the third by eleven, the fourth by seven, the fifth by two, the sixth by one, the seventh and eighth by none, and the ninth by one case.

Relation to inflammatory conditions. The frequent occurrence of carcinoma of the appendix as shown by the above analysis in the earlier years of life has been noted by all who have investigated this subject. This has led to the general opinion that the inflammatory lesions of the appendix which occur so commonly in the same period have some etiological relation to the new growth. Letulle and Weinburg especially have emphasized the relation of cancer to chronic obliterative appendicitis. Their view is exceedingly plausible for the appendix is a vestigial organ and it is well known that in such, as well as in atrophied organs, lawless growth of epithelium is prone to occur. Chronic obliterative appendicitis is usually accompanied by some atrophy and considerable displacement of epithelial elements. Under such circumstances irregular growth of epithelium in the midst of the irregular connective tissue proliferation could readily be understood. There is however as yet insufficient evidence to support this view. Aside from Letulle and Weinburg's four cases, in but two is an obliteration of the lumen mentioned and in these it is not clear whether the obliteration preceded or was the result of the new growth. In one of our cases it was impossible to determine this point. In five other cases a definite microscopic diagnosis of chronic appendicitis is made. It is of interest also that a large proportion of the cases give a history of previous attacks referable to the appendix. On the other hand in a larger number of cases the tumor gave rise to no symptoms or to but one acute attack. It is obvious therefore, that while it is possible that cancer of the appendix may bear some relation to chronic inflammatory disturbance of the organ, further detailed investigations are necessary before it can be determined whether the latter are the cause or the result of the new growth.

PATHOLOGY.

Location of tumor. The location of the tumor is more or less definitely stated in twenty of the descriptions; in twelve it occurred at the distal end usually at the tip of the organ, in three at the base, in two in the middle third and in three it involved the caecum. In these last it is possible that the point of origin was in the caecum.

Gross appearance. The tumor in most instances was obscured by acute inflammation or in an obliteration of the lumen of the appendix and therefore was not recognized upon macroscopic examination; such was the case in each of the three cases here reported. In those reports accompanied by a gross description, the new growth is usually described as a firm white nodule. The size of the tumor varies considerably; the larger ones are described variously as of the size of a marble, a pea or a cherry pit; others measure from five to thirteen millimetres in diameter. Occasionally no distinct tumor is evident but merely a localized thickening of the wall, or more frequently, an obliteration of the lumen indistinguishable from a chronic obliterative inflammation.

Histology. Seventeen tumors have been described as carcinoma simplex, alveolar or spheroidal cancer; in one of these the qualifying adjective, medullary, was used and in one, scirrhus. Eight have been termed adeno-carcinoma or cylindrical cell cancer, two colloid and seven merely carcinoma. The predominating type of tumor therefore appears to be the simple alveolar cancer.

Extension, Metastases and Recurrence. Appendiceal cancer shows little tendency to invade other tissues. Three cases of involvment of the caecum have been reported. In one (Jones and Simmons) the invasion of the caecum was slight; in another (Beger) a tumor the size of a walnut projected into the caecum and metastases were found in the retroperitoneal glands; in

Elting's case, the adjacent coils of small and large intestine were affected as were also the lymph nodes. With these exceptions, cancer of the appendix appears to have little tendency to extension; the growth being limited as a rule to submucosal and muscular coats. In Norris' case and in Case II here reported a tendency to extend into the meso-appendix was observed. Metastases have been described only in the two cases of Beger and Elting just cited. Little information concerning recurrence of the tumor after removal is available. Few reports contain the after history of the patient and indeed the majority of reports are so recent that sufficient time has hardly elapsed for observations on this point. Rolleston, on account of the poor health of his patient several months after operation, suspected a recurrence. Wier's patient was in good health three years after operation. Harte and Willson quote a personal communication from Hurdon stating that her patient was in good health two years after operation, with no evidence of recurrence. Moschcowitz had occasion to open the abdomen of his first patient one and one-half years after removal of the appendix and found no evidence of recurrence of carcinoma at the site of the previous operation.

Associated Lesions. These include practically all the acute and chronic inflammatory conditions which may affect the appendix. Acute lesions were present in twelve of the cases cited above, and include suppurative, ulcerative and gangrenous appendicitis, periappendiceal abscess and peritonitis. The chronic lesions in thirteen cases include chronic interstitial and obliterative appendicitis, chronic periappendicitis and organization about chronic abscess. Not infrequently acute and chronic lesions were associated. A sinus discharging externally was present in each of two of the cases of periappendiceal abscess. Perforation is noted in two cases. In one, discovered at autopsy, a general peritonitis was present; in the other, at operation, a brownish fluid with faecal odor escaped on opening the peritoneum. Elting's case of colloid cancer, found at autopsy, showed rupture without evidence of inflammation. Enteroliths have been noted in a few instances.

Clinical History. On examination, the clinical data accompanying the cases here recorded shows that appendiceal carcinoma gives rise to no peculiar symptoms; the symptoms demanding operation have in all instances been those of the associated acute or chronic inflammation. An analysis gives the following results: Six tumors discovered at autopsy, death being due to other causes, with no history of symptoms referable to the appendix; six discovered while operating for the relief of symptoms referable to disease of the pelvic organs, and twenty-two in which the operation was done on account of symptoms more or less definitely those of appendicitis. Of the latter in two no details of the clinical history are given; in four there is a history of a single sharp attack; in ten a history of recurrent appendicitis with from two to four definite exacerbations and in six a history of symptoms referable to the appendix and covering a considerable period of time. It is worthy of note that in all cases which demanded operation the symptoms were those of inflammation of the appendix. The four cases in which no inflammation was found were among those discovered at autopsy or during operation for disease of other organs. It would seen therefore justifiable to conclude that the tumor itself while limited to the appendix gives rise to no pathognomonic symptoms; all manifestations demanding operation are those of the associated inflammation.

CONCLUSIONS.

1. Primary carcinoma of the appendix is present in from one-third to one per cent. of the appendices removed at operation; its discovery at autopsy is very unusual.

2. It is a tumor of early life, occurring usually between the ages of ten and forty; the largest number being in the third decade.

3. It occurs with equal frequency in either sex.

4. Acute or chronic inflammatory lesions are usually present and are responsible for the symptoms demanding operation; the tumor itself while localized gives rise to no pathognomonic symptoms.

5. Direct extension to other organs and metastasis are rare.

6. The usual type is the simple alveolar cancer; adeno-carcinoma occurring next in frequency, while colloid cancer is unusual.

7. Conclusive information concerning the relation of this lesion to other diseases of the appendix can only be obtained by the careful routine histological examination of all appendices removed at operation.

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RETENTION CYST AND DIVERTICULUM OF THE VERMIFORM APPENDIX.

BY ERASTUS CORNING.

(From the Bender Laboratory, Albany, N. Y.)

Retention cyst of appendix.—The recognition of retention cyst, known also as cystic dilation, hydrops and mucocele of the appendix, is generally ascribed to Virchow,[1] who characterizes it as simple cyst caused by the retention of mucus in an organ, partially or completely obliterated in its proximal portion. Virchow, however, refers to Rokitansky's[2] earlier observation that an obstruction of the appendix leads to an accumulation of colloid material and a cystic condition which he terms hydrops of the appendix. Some of the lesions of the appendix reported at about this time as tumor would appear rather to be retention cysts. Virchow states that he considers the colloid tumor described by Gähtgens in 1853 to be such. There is also some doubt concerning the nature of the tumors of the appendix reported by Rokitansky[3] in 1867 as colloid cancer. The gross descriptions of these accurately characterize cystic dilation and in the absence of microscopic examinaton there is reasonable doubt as to whether they are examples of cancer or cyst.

The subject of cystic dilation has never attracted much attention, probably because it is never recognized clinically and also because pathologically it is generally considered to be merely an unusual form of chronic appendicitis. Still the literature contains many reports of cases. Van Hook[4] in 1896 was able to collect thirty-two cases in which the condition was found either at autopsy or operation; a cursory review of the literature indicates that to date only about sixty cases have been reported. The largest number reported by a single investigator are the six described by Ribbert[5] in 1893. Statistics based on autopsy material indicate, however, that it is not very infrequent. Ribbert's cases were found in the course of 400 post mortem examinations. Bryant[6] found one in 124 autopsies, Steener[7] three in

2,286 autopsies, Boody[8] one in 528, and Christian[9] sixteen in 3,770. These figures, however, give no information concerning the frequency of cystic dilation as compared with other diseases of the appendix as seen at operation and as far as I am aware, no series showing such incidence exists. On this point the records of the Bender Laboratory offer some definite information. During a period of somewhat less than nine years 735 appendices removed at operation have been examined; five or 0.68 per cent. were examples of cystic dilation. These figures and those of Christian, which gave 0.42 per cent. for autopsy material, indicate that this lesion is relatively not infrequent.

The size of the tumor is variable. Virchow mentions a dilation the size of a man's fist; Kelly[10] describes one the size of a small orange; and Guttman[11] one fourteen centimetres in length and twenty-one centimetres in its greatest circumference. As a rule, however, the size is stated to be that of a walnut, a goose egg, a hen's egg or a small sausage. The smaller localized protrusions occasionally described are in all probability divertcula.

The gross appearance of the cyst varies according to the location of the constriction. If the latter is at or near the caecum the cyst appears to be more or less continuous with the caecum and may have a tendency to an erect position. Occasionally the intra-appendiceal pressure may cause the cyst to protrude into the caecum. When the obstruction is some distance from the caecum the cyst has the appearance of a tumor with a pedicle connecting it with the caecum. Very rarely two cysts may develop. The walls may be thick and firm or thin and translucent. Adhesions to adjacent organs are common. The shape of the cyst is as a rule cylindrical, unless the structure is near the tip. Kelly and Hurdon[12] describe an appendix which was seen at operation six years before its removal. At that time in the median portion was a single cyst with obliteration of the lumen beyond. Upon its removal after six years three cysts separated by fibrous partitions had formed; the later ones had developed in the proximal portion. The material within the cyst is, as a rule, a thick gelatinous substance so tenacious that, as Virchow states, it may be picked up with forceps and cut with scissors. As a rule this substance is more or less turbid, but occasionally it is distinctly translucent and of a greenish yellow color. Sometimes thin watery clear fluid or a thicker milky fluid is found. The material may be blood stained. The consistence of the fluid depends on the functional activity of the mucosa and is therefore an index of the degree of atrophy of the latter. If the cyst becomes infected, suppuration (empyaema of the appendix) may result.

The mucosa is usually smooth and glistening with evidence of atrophy due to mechanical pressure. The finely granular velvet like surface due to the presence of lymphoid tissue is absent. Histologically the picture is that of a chronic inflammation and atrophy. Submucosa and lymphoid nodules have as a rule entirely disappeared. The mucosa is very thin, seldom contains glands and is usually represented by a layer of low columnar or cuboidal epithelium. In the muscular coat fibrous thickening, often hyaline, occurs, and infiltration of lymphoid cells is common. Occasionally small strands of fibrous tissue may bridge the lumen irregularly.

Cystic dilation is usually due to a chronic appendicitis in which, in the process of healing, opposing denuded surfaces become fused together and cause obliteration of the lumen. The secretion in the distal end accumulates and as there is no outlet a cyst results. The following description by A. O. J. Kelly of repair of appendiceal inflammation puts the matter very accurately: "That portion of the wall of the appendix which is the seat of erosion or ulceration is replaced by newly formed connective tissue, which like all newly formed connective tissue, tends to contract and to form cicatricial tissue. As a consequence the lumen becomes contracted. If there have been several points of ulceration, there will also be several points of stenosis of the lumen. Depending upon the situation, size, and shape of these cicatrices, there results either a transverse narrowing of the lumen, or, particularly if the cicatrix be longitudinal rather than annular, there will ensue a shortening of the organ along one side—a curling up of the appendix, or an angulation, flexure, twist, etc. If there be several cicatrices, the utmost distortion of the appendix may be produced. On the other hand, there may be complete obliteration of the lumen of the appendix at one or more points along its length. It is readily conceivable that in the event of annular ulceration, granulating surfaces being everywhere opposed to granulating surfaces, these adhere, and, as the processes of regeneration and organization go on, become permanently united by means of newly formed connective tissue. Such obliteration of the lumen may be circumscribed or generalized. In the latter case obliterating appendicitis results; in the former merely a local obliteration. The latter may be situated anywhere, and not uncommonly gives rise to a condition known as cystic dilation, retention cyst, hydrops, or mucocele (Fere) of the appendix. The development of this condition of cystic dilatation of the appendix depends upon several factors. The obstruction of the lumen must be complete, or almost so: the obstruction or obliteration must have obtained at a time when the affected portion of the organ contained no pathogenic micro-organisms, the mucus membrane of the affected portion must be intact, or at least capable of functionating; and the secretion by the mucus membrane must be more rapid than the absorption from the portion of the appendix involved. If the obstruction be not complete, the secretion is likely to be forced through even a narrow opening with sufficient rapidity to prevent a large accumulation, and, on the other hand, infection is likely to occur through the patulous lumen, converting a cystic dilatation into an empyaema. If there are already virulent bacteria in the affected portion of the appendix, an empyaema, of course, rather than a cystic dilatation, will develop in the first place. If the mucous membrane is incapable of functionating, there can be no accumulation of fluid, and the same is also true if absorption be more rapid than secretion."

It is a matter of interest that in a case reported by Gruber[13] a tuberculous ulcer apparently aided in bringing about complete stricture of the appendix.

It is obvious that it is only in connection with inflammatory obliteration of the lumen—a formation of synechia similar to that seen in various cavities of the body—that retention cyst can develop. It cannot develop in that form of obliteration which Ribbert and others regard as an involution process in a vestigial functionless organ for in such appendices the obliteration begins at the tip and gradually involves the entire organ; there is, under such circumstances, no possibility of the retention of secretion.

Not all cases, however, are due to obliteration of the lumen. A cystic condition may be caused, as in the case reported by Treves and Swallow by a twist, kink or angulation of the appendix. Periappendiceal adhesions may assist in maintaining such a condition.

Other forms of cyst as the hydatid reported by Lafforgue and the subserous cyst mentioned by Christian do not come within the scope of this communication.

Clinically, cystic dilation gives rise to no pathognomonic symptoms and the condition is usually mistaken for some other form of appendicitis or is discovered accidentally. A palpable tumor in the right iliac fossa, as in the cases of Wier[15] and Landenberger[16] should, in the absence of acute symptoms, cause retention cyst to be considered. Aside from this the symptoms are usually obscure or suggestive of chronic appendicitis. Wood[17] has called attention to the possibility of mistaking the tumor for floating kidney and also to the danger of rupture by taxis when the cyst is in an inguinal hernia. Such an accident is reported by Van Hook. Wölfer and McArthur[18] each report a case of cystic appendix in the sac of a hernia.

There appears to be no relation between cystic dilation and cancer of the appendix, though both have an interesting relation to obliterative lesions. In a small proportion of the cases of cancer the tumor develops in an obliterated portion of the appendix, usually the tip of the organ. Obliteration at this point is, however, as a rule that due to involution rather than to inflammation. The only cystic carcinoma limited to the appendix, is the case of colloid cancer reported by Elting,[19] if we exclude Rokitansky's cases, which in the absence of microscopic examination appear to be retention cysts. On the other hand Elting's tumor appears to be a primary lesion, for in the description, no mention is made of an obliteration of the proximal portion of the appendix. Furthermore, in cystic dilation the changes in the epithelial cells are those of atrophy rather than of proliferation.

Diverticulum of the appendix.—The condition known as diverticulum of the appendix has attracted but little attention. Ribbert appears to have been the first to report this conditon. He describes a retention cyst on the surface of which, at the mesenteric border, was a group of small cysts which he considered to be caused by the cystic dilatation of glands in the mucosa. Kelynack[20] reports a somewhat similar condition in which two diverticula were directed beneath the folds of the mesentery. Hawkins mentions an appendix with five or six diverticula. Kelly and Hurdon refer to a case in which the diverticulum was associated with retention cyst. Edel,[21] Fischer,[22] and Hedinger[23] each report single cases of diverticulum; Lejars and Menetrier,[24] two cases; and Mertens,[25] three cases in a series of 139 specimens examined.

In the cases above quoted, cystic dilation of the appendix existed in four, cancer in one, and tuberculosis in one. Periappendicular adhesions are frequently mentioned. Lejars and Menetrier describe an acute inflammation affecting the diverticula in one of their cases; to this condition they give the name of "appendicite diverticulaire." The size of the diverticula varies. In some cases they were found only on histologic examination; in others they are small nodular protuberances on the surface of the appendix. Lejars and Menetrier describe them as hemispherical elevations varying in size from that of a raisin to a small pea. The largest apparently is that of Fischer, which measures 11 x 12 millimetres.

It is a general rule that diverticula of various portions of the intestine occur in individuals past middle life; to this rule diverticulum of the appendix is not an exception. The age is given in seven of the twelve cases collected by Hedinger; in five of these it varied from sixty-six to seventy-five; in one it was forty-seven and in another fifteen. Ribbert states that the lesion which he reports occurred in an old man, while Fischer's was in an individual about fifty. On the other hand the appendix described by Hedinger was that of a newly-born child.

Most if not all of the diverticula of the appendix belong to the group of false diverticula, that is, they are a protrusion of the mucosa and submucosa through the muscular coat. The wall of the sac therefore has no muscular coat thus differing from true diverticula in which all coats are represented. False diverticula, as far as is known, are acquired and never congenital. It is of interest therefore to consider the conditions in the appendix which may be concerned in the etiology of diverticula. The association of obstructed lumen and cystic dilation in five of the cases, including the one here reported, strongly supports the theory which ascribes the chief influence to increased intra-intestinal pressure; in this instance, of course, intra-appendiceal pressure. Likewise the frequency with which the processes penetrate the mesentery supports those observations which indicate that the diverticulum forms at the point of least resistance, that is along the sheath of a blood vessel (vein) passing from the intestine into the mesentery.

Traction is not believed to be a common cause of diverticulum though true diverticula of the intestine have several times been described as the result of traction exerted by accessory pancreas or connective tissue bands. Such traction on the appendix associated with inflammation, or the pressure of faeces, might lead to pressure atrophy of the mucosa and muscularis and a condition analagous to false diverticulum.

That diverticulum of the appendix may be congenital has been definitely determined by Hedinger's observation of the condition in a newly-born child.

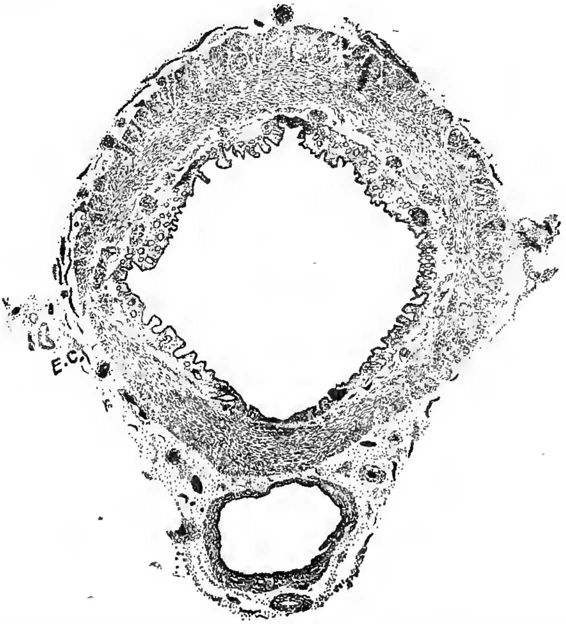
REPORT OF CASES.

The records of the Bender Laboratory covering a period of nine years contain descriptions of 735 appendices removed at operation; among these are found four examples of cystic dilation, with also, in one, a peculiar form of diverticulum. Other diverticula of lesser degree may have occurred during this period, but if so have not been sufficiently characteristic to attract attention. The descriptions of these appendices follow:

Case I.—Records of the Bender Laboratory, Surg. Path. No. 49:60.

Clinical History—Mr. B., aged 16, admitted to the Albany Hospital. Service of Dr. W. G. Macdonald, February 16, 1900. *Past history*—Negative. *Family history*—Negative. *Present illness*—Six weeks ago and again three weeks ago well-marked attacks of appendicitis, the second lasting two weeks. Attacks began with diffuse pain, starting in the region of the stomach, finally localizing in the right side. *Clinical diagnosis*—Chronic appendicitis. *Operation*—February 17th; uneventful recovery; discharged March 3d, cured.

Pathological Examination.—Gross Description—The specimen consists of an appendix removed at operation. It is 6 cm. in length; the proximal portion for a distance of 3 cm. averages 7 mm. in diameter; the distal half is much enlarged, and measures from 13 to 16 mm. in greatest transverse diameter. The vessels of the peritoneal covering are much congested. The enlarged distal portion is distinctly cystic and on pressure a small quantity of mucoid material can be expressed through the narrowed lumen of the proximal portion of the appendix. The dilated portion of the appendix is found to contain a considerable amount of gelatinous mucoid material. On the side opposite the mesenteric attachment, the walls of the appendix are distinctly hypertrophied and the mucous membrane is thickened. Along the mesenteric attachment in the upper portion of the cystic enlargement the walls of the organ are greatly thinned and at one point is a minute opening 2 mm. in diameter, which is plugged with mucoid material. On this side of the appendix the mucosa appears to be entirely atrophied for some distance. A similar atrophy of the muscular coat over a small area is also evident. Again at a lower point the material in the lumen of the appendix appears to have destroyed by pressure all portions of the wall except the peritoneal coat and has separated the peritoneum from the muscle for a short distance, forming a small cystic cavity 4 mm. in diameter, the walls of which are somewhat irregular. At a point 14 mm. from the beginning of the dilation of the appendix the lumen rapidly narrows until it measures but 2 mm. in diameter. This condition extends for a distance of about 4 mm., when the lumen again enlarges to form a dilation 8 mm. in length, and 7 mm. in transverse diameter. The walls surrounding this area of dilation are hypertrophied and the mucous membrane in some places is somewhat thickened, in other places apparently atrophied. Toward the tip of the appendix the dilation of the lumen ceases; the lumen of the extreme tip is obliterated.



Illustrates lesions of Case I. Larger cavity is that of cystic appendix with marked atrophy of mucosa and submucosa; smaller cavity is the diverticulum in the mesentery. (x 6.)

Anatomical Diagnosis—Chronic appendicitis with cystic dilation of distal end.

Histologic Description—Sections through four different levels of the cystic dilation were studied. Unfortunately no sections were taken through the constricted portion. To the naked eye sections from each level show in the attached mesentery a circular opening, which at first glance apparently a blood vessel, proves when placed under the microscope to be a cavity lined by a mucosa similar in every respect to that of the appendix proper. This diverticulum varies in diameter in the hardened and stained preparation from 0.15 to 0.35 cm; its form is almost uniformly circular though occasionally oval.

The lumen of the appendix proper is dilated, and that portion of its wall most distant from the mesentery is much thickened. The lumen is free except for small masses of mucoid material adherent here and there to the mucous membrane. The character of the latter varies at different levels, but atrophy is everywhere a prominent feature of the lesion. The surface epithelum is of the cylindrical goblet cell type and forms an unbroken ring about the entire circumference of the appendix. This surface epithelium is directly continuous with that of the glands opening into the lumen. These glands are all lined by the same tall cylindrical cells with clear periphery. Many of the glands are small and irregular; others are dilated, forming small cysts in the mucosa. Opposite the diverticulum they have almost entirely disappeared. The interglandular tissue of the mucosa is rich in eosinophiles. The lymphoid nodules are very small, appearing usually as narrow elongated patches; on the mesenteric side they are entirely absent. The submucosa is very indistinct and slightly infiltrated with lymphoid cells and eosinophiles, as are also the muscular coats and the subserous tissues. The blood vessels of the latter are numerous and greatly congested. On the mesenteric side, between the diverticulum and the appendix proper, the muscular coat is much thinner than on the opposite side.

The diverticulum lies outside the muscular coat in a loose vascular adipose tissue freely infiltrated with lymphoid cells. The mucosa of the diverticulum is very similar to that of the appendix itself, though the glands are smaller and fewer in number, and the surface epithelium is not so markedly of the "goblet cell" type. A delicate muscularis mucosa, and submucosa are evident, as are also a few small accumulations of lymphoid cells, which however bear no resemblance to lymph follicles. Eosinophiles are numerous. No muscular coat can be seen at any level; the diverticulum is thus of the type characterized as false.

Microscopic Diagnosis—Chronic appendicitis with cystic dilation and false diverticulum.

By comparing the gross and histological appearances it is apparent that this diverticulum ran through the greater portion of the cystic dilation. Unfortunately owing to the fact that it was not recognized upon gross examination its exact length and its mode of termination cannot be determined. It appears justifiable to conclude that the small opening plugged with mucus at the upper portion of the dilation noted in gross examination was the point of origin. From here it passed apparently through the muscular coat and instead of protruding any distance into the meso-appendix, passed downwards in close relation to the muscular coat. As it is seen in four different sections taken at various levels of the dilation it must have passed almost to the tip of the organ which would give it a length of about three centimetres. Whether it terminated blindly or communicated again with the lumen of the appendix cannot be determined. The possibility of the latter is suggested by the small irregular dilation of the end of the appendix noted in the gross description.

Case II—Records of the Bender Laboratory. Surg. Path. No. 49:76.

Clinical History—Mrs. G., aged 50, patient of Dr. Albert Vander Veer, Albany Hospital. *Family history*—Negative. *Past history*—Always more or less constipated. *Present illness*—For the past three or four years has had colicky pains in right lower abdominal region. Three months ago the patient had a well defined attack of appendicitis, with constipation, pain and vomiting. Enemata were given, and the patient made a good recovery. An operation was advised, but postponed temporarily.

Operation by A. Vander Veer, December 26th. On opening the abdominal cavity, a small amount of serous fluid escaped. The appendix was found back of the caecum and bound down by adhesions.

Pathological Description.

Gross Description—Specimen consists of the distal 3 cm. of an appendix. The proximal end has very thick walls and the lumen is almost entirely obliterated for a distance of 5 mm. Below this the organ is enlarged, averaging 14 mm. in diameter. There are a few adhesions over the serous surface. The peritoneum is injected, and there are a number of discrete and confluent pin-point subperitoneal haemorrhages. At one place the wall is thin, and presents a perforation 3 mm. in diameter with irregular edges. (This perforation was produced artificially after removal of the appendix.) On section the mucous membrane of the distal 2.5 cm. is pale and covered with a yellowish, almost transparent jelly-like colloid material. The remainder of the mucous membrane is smooth and free from this material. The walls of the organ are considerably thickened. The musculature averages 4 mm. in thickness. In the neighborhood of the perforation the wall is very thin, the mucous membrane and musculature have entirely disappeared over an area 4 mm. in width. The mesentery, which accompanies the specimen, is deeply congested.

Accompanying the specimen was a large mass of colloid material, yellowish red in color; and distinctly striated. The reddish color present is apparently due to the presence of blood or blood pigment.

Anatomical Diagnosis—Chronic obliterative appendicitis with cystic dilation.

Microscopic Description—A section through the proximal end shows the normal structures of the appendix to be entirely obliterated by a chronic inflammation, which leaves only a narrow slit-like opening lined by a very low cylindrical epithelium. The glands and lymph nodules have been entirely destroyed, and the submucosa has been replaced by a dense connective tissue more or less hyaline in character. The muscular coat is very thick and replaced in part by fibrous tissue. Lymphoid cells are numerous throughout all coats. The serous coat is thickened and adherent to it are numerous vascular fibrous tags. In the submucous, muscular and serous coats of a lower level is seen the same chronic inflammatory condition as in previous section. In the center of the section is an irregular lumen much smaller than normal, which contains blood stained colloid material. The mucosa consists of low irregular papillary projections lined by three or four layers of cylindrical cells; no glands are present.

A section through the point of greatest dilation shows an area of chronic ulceration in intimate contact with the colloid contents of the lumen. The colloid material which stains deeply with haematoxylin is clear and hyaline with a more or less stratified arrangement, and contains no cells.

Case III—Records of the Bender Laboratory, Surg. Path. No. 49:212.

Clinical History—Mr. D., aged 36, admitted to the Albany Hospital, service of Dr. Albert Vander Veer, on June 9, 1902. *Family and past history* negative. *Present illness*—Attacks of sudden abdominal pain in August, 1901, and four similar attacks since. Now presents symptoms of acute appendicitis. Operation June 10th; appendix deep in pelvis and firmly bound by adhesions.

Pathological Examination—Gross description—Specimen consists of the distal portion of the appendix vermiformis, and is 4 cm. in length and irregularly distended. The outer wall is roughened with blood stained fibrous adhesions. The diameter of the tube at proximal end is 1.5 cm. On section the lumen of the appendix is found to contain a colloid substance, which can easily be expressed; the wall is thickened. The mucous membrane appears thickened and oedematous, and near the tip the mucous membrane forms a small pouch-like dilation, which is filled with colloid material.

Anatomical Diagnosis—Chronic appendicitis with localized cystic dilation.

Histological Examination—Two sections through proximal portion of the appendix show evidence of chronic inflammation involving all coats of the organ. The serosa is thickened, and to it are adherent numerous vascular tags of fibrous tissue. The mucosa is atrophied and contains a few small irregular glands widely separated; the surface epithelium has almost entirely disappeared; the lymphoid nodules are small and irregular. The lumen contain a colloid material with fragments of desquamated epithelial cells. A section through the dilated portion shows the same general condition, and in addition, a cavity 4 mm. in diameter between the muscular and serous coats. This latter cavity contains a material which is similar to that in lumen of appendix, but is richer in cell debris and contains red blood corpuscles. Its epithelial membrane has almost entirely disappeared, but here and there are small accumulations of cuboidal epithelium; no glands are evident. The surrounding tissue is freely infiltrated with lymphoid and plasma cells and a few polymorphonuclear leucocytes. Much old blood pigment is present. This cavity is apparently the periphery of the cystic dilation mentioned in the gross description; unfortunately, the section does not pass through opening into appendix proper.

This case presents a few points of peculiar interest. No cause for the retention of secretion was evident either upon gross or histological examination. A constriction may have existed at the junction of appendix with caecum, or a twist may have been present. Unfortunately the clinical notes contain no reference to the conditions found at operation other than that the appendix lay in the pelvis and was bound down by adhesions. The histological picture, however, justifies the diagnosis of cystic dilation. The small pouch at the distal end must be considered as a false diverticulum. In view of the observations of Lejars and Menetrier concerning "diverticular appendicitis" it is of interest that in this pouch we have an ulcerative inflammation which though of a chronic character is more active than that in the appendix proper.

Case IV—Records of the Bender Laboratory, Surg. Path. No. 04:123.

Clinical history—Mrs. H. T., aged 60, admitted to the Albany Hospital, service of Dr. A. W. Elting, February 18, 1904. *Family history*—Father living. Mother died at 22 after amputation of knee for tuberculosis. *Past history*—Had pneumonia in 1891. Has had two living children and one miscarriage. Always had painful menstruation. Menopause at 47. *Present illness*—About 25 years ago patient noticed a pulsating tumor in median line of abdomen, and on exertion had severe pain in epigastrium and thorax with dyspnoea. At the same time she had occasional attacks of vertigo, but never became completely unconscious. In August, 1903, she was confined to bed for three weeks after severe attack of pain in the abdomen. At this time the pulsation disappeared, though swelling remained in median line of hypogastrium. There was difficulty in micturition and defaecation. Micturition was frequent. Appetite good. No history of vomiting.

Patient on admission was found to be a very small framed, poorly developed and poorly nourished woman. Skin and mucous membranes pale. Pulse 100; low tension; poor quality. Wall of artery somewhat thickened. Lungs slightly emphysematous. Heart negative. Abdomen decidedly prominent, particularly in the lower portion. Prominence appears to be symmetrical, and seems to emerge from the pelvis. On palpation a large tumor mass can be felt, which apparently occupies the entire pelvis and projects upward to about the level of the umbilicus. This tumor is of rather firm consistence and somewhat irregular outline. It does not appear to be at all moveable. There is some tenderness on palpation over the tumor. Distention of the intestines is evident, and the action of the bowels has been extremely sluggish. *Operation,* February 20th. Median incision between the umbilicus and pubes exposes a cyst lying in the pelvis and found to be adherent to adjacent structures. On opening the cyst about 1,000 cc. of semi-solid gelatinous material can be removed. Left tube and ovary removed. Dilated appendix with a portion of caecum, supposed to be a colloid cancer of the appendix, dissected away.

The patient recovered satisfactorily from the shock of the operation, and her convalescence was uninterrupted.

Pathological Examination—Gross description—Material received as two separate specimens. Smaller specimen is an appendix, the distal end of which is enlarged to form a globular cyst 3.5 cm. in diameter. The proximal portion 3.5 cm. in length has an outside diameter of from 0.8 to 1.2 cm., and has a patent lumen. The entire specimen is covered with blood stained fibrous tags. The wall of the cystic portion is 2 mm. in thickness, while that of proximal portion measures 3 mm. The cyst contains an amber colored jelly-like material. Specimen not further examined, but placed in fixation fluid.

Larger specimen consists of approximately 1,200 cc. of thick dark amber mucoid material and a collapsed cyst wall. The latter when distended measures 14 cm. in its greatest diameter. Its wall is 1 to 2 mm. in thickness. Attached to this piece of cyst wall by bands of fibrous tissue is a portion of normal Fallopian tube 6 cm. in length.

Anatomical Diagnosis—Colloid cyst of appendix. Unilocular cyst of ovary. Normal Fallopian tube.

Microscopical Description, Appendix—Lumen greatly dilated. Mucosa and submucosa atrophied. Mucosa is so stretched that tubules are very shallow or entirely obliterated, and form a continuous layer with irregular projections into the submucosa. No isolated glands are present. The epithelial cells are elongated, compressed and practically all of the goblet cell type. In some places the glandular appearance is entirely lost, and the lining epithelium consists of but a single layer of low cuboidal cells. The lumen is filled with an almost homogeneous hyaline material, which stains faintly with haematoxylin. The lymphoid nodules are atrophied and few in number. The muscular coat shows increase of connective tissue and slight infiltration of lymphoid cells.

Microscopic Diagnosis—Colloid retention cyst of appendix.

In this case as in the previous one the cause of the retention is not apparent. The portion of appendix received from the surgeon showed the lumen of proximal end to the patent and the description of the operation makes no mention of obstruction. It is possible that the large ovarian cyst may, by pressure, have caused an obstruction or kink of the appendix, but on this point there is no information.

The following case of colloid deposit about the appendix, though it illustrates neither cystic dilation nor diverticulum, is believed to be of some interest because of the possibility of confusing it with a ruptured cystic appendix.

Records of the Bender Laboratory, Surg. Path. No. 58:119.

Clinical History—Mrs. B., aged 40, admitted to the Albany Hospital, service of Dr. W. G. Macdonald, on September 2, 1903. *Family history*—

Father and brother died of tuberculosis. No history of cancer. *Past history*—Patient had the usual diseases of childhood. Her menstruation began at 13, and has always been regular. She had two children and one miscarriage. She had "inflammation of the bowels" at the age of 12 years. At the age of 20 she was troubled by bleeding from the bowels. For the past two years patient has suffered from indigestion. She has always been more or less constipated. *Present illness*—On the 28th of July the patient felt perfectly well and spent most of the morning out of doors. She ate a hearty dinner, and at three o'clock in the afternoon was taken ill with severe pain in the right iliac region. At this time she vomited once. In a short time she complained of pains throughout the abdomen. At midnight she took an enema with good results. The next day a physician was called, who made a diagnosis of chronic appendicitis with pelvic inflammatory disease, and advised operation.

Operation, September 3d, by Dr. W. G. Macdonald. Incision in the median line between the symphysis and umbilicus. The appendix was found bound down by adhesions. There was an ovarian cyst on the right side. Operation consisted of repair of the cervix, curettment of uterus, clamp cautery for haemorrhoids, right salpingo-oöphorocystectomy and appendectomy.

Pathological Examination—Gross description—Material to be examined consists of appendix and Fallopian tube with broad ligament.

The appendix is of normal size with mesentery attached. The peritoneal surface is blood stained and congested. All coats are greatly thickened; the mucosa is swollen. At tip, externally, is an accumulation of thick colloid material intimately adherent to appendix and apparently covered by peritoneum. No evidence of rupture or perforation.

The Fallopian tube is swollen, and its walls thickened, its peritoneal surface injected, and its lumen contains a thin purulent fluid. Near distal end in the broad ligament is a thin walled cyst 6 cm. in diameter, containing clear slightly yellow mucoid fluid. Ovary absent.

Anatomical Diagnosis—Colloid mass about tip of appendix. Cyst of broad ligament; chonic salpingitis.

Microscopic Examination—Appendix—The mucosa and submucosa are normal. The muscular coat appears to be greatly thickened. Intimately adherent to the serosa, and equalling the section of the appendix in size, is a roughly circular mass of colloid material taking a faint haematoxylin stain. This mass is partially organized, having an alveolar appearance, due to septa of new formed connective tissue. Numerous new formed blood vessels penetrate the mass at various angles, and there is considerable infiltration with lymphoid cells and polymorphonuclear leucocytes. Adherent to this mass and connecting it with the appendix, as well as to the adjacent adipose tissue, are strands of newly formed connective tissue.

Fallopian tube—Lumen contains pus cells and granular material. Papillary processes largely destroyed; those remaining are infiltrated with lymphoid cells and leucocytes. This infiltration extends through all the coats. The serosa is thickened and edematous.

Microscopic Diagnosis—Organizing mass of colloid adherent to appendix. Chronic salpingitis.

At first glance the condition just described was supposed to be either a ruptured colloid cyst of the appendix or a colloid cancer. Careful gross examination ruled out the first and microscopic examination the latter. The absence of either acute or chronic inflammation of the inner coats of the appendix would contraindicate an explanation based on the supposition of a previous rupture. The appearance of the mucosa was not that of retention cyst. It is apparent, therefore, that the material about the appendix can be considered only as an accumulation resulting from the rupture of a colloid cyst elsewhere in the abdomen. A cyst of the ovary or broad ligament would appear to be the most probable source. The operator noted a cyst on the right ovary and the gross examination of the tube revealed a cyst of the broad ligament. It is possible that a third cyst, which in its collapsed state, escaped observation may have been the source of the colloid material. The sudden attack of severe abdominal pain, in the absence of previous symptoms, is very suggestive of the rupture of a cyst with the escape of its contents into the abdominal cavity. The degree of organization in and about the colloid material was about what would be expected in the period which had elapsed.

Rupture of ovarian cysts leading to interesting secondary lesions in the abdomen, although by no means common, is a well understood condition. The localization of the cyst contents about the appendix and its discovery at operation are, however, very unusual.

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THE ELIMINATION OF ENDOGENOUS URIC ACID IN A CASE OF CHRONIC GOUT.*

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During the past few years as the result of numerous investigations of uric acid metabolism, views concerning uric acid formation have been greatly modified. The theory, once almost universally accepted, that in mammals, uric acid is a product of the metabolism of all albumins and represents a stage preceding the formation of the end-product, urea, has been abandoned. A considerable number of definite new facts has been established and new theories have been brought forward to explain them.

Only a brief summary of the more important points in regard to this work will be given here. For more complete information and for references to the extensive literature the reader is referred to reviews by Baumgarten, Futcher and others.[1]

According to recent views the uric acid eliminated by the normal human body when the individual is on a mixed diet is from two sources; that from the food, which is called the "exogenous" uric acid; and that from the metabolic processes of the individual which is known as "endogenous" uric acid. The same terms, first used by Burian and Schur,[2] apply also to the bodies closely related to uric acid known as the xanthin or purin bases. Uric acid and purin bases together are called "purin bodies" or "purins." It is stated[3] that of the purins eliminated in the urine nine-tenths are present as uric acid and one-tenth as purin bases. Kaufmann and Mohr,[9] however, find variations in the relations of uric acid to total purins.

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As a result of the work of Mares,[4] Horbaczewski,[5] and others, the exogenous purins in the urine of mammals are believed to arise, not from the decomposition of all albumins, but only from the nucleins and the preformed purins which they contain. The other nitrogenous elements of the food are said to produce no uric acid or purin bases in the urine.

More recent investigations, particularly those of Burian and Schur,[6] Siven,[7] and others, have led to general conclusions regarding the formation and elimination of exogenous and endogenous uric acid. The validity of some of these conclusions may fairly be questioned.

According to these investigators the endogenous uric acid and purin bases found in the urine arise from metabolic processes which go on independently of the amount or composition of the food, *e. g.*, from the destruction of the nuclein of body cells.

Burian and Schur have also claimed that the exogenous and endogenous uric acid and purins found in the urine of man can be separately and accurately determined. From analysis and experiment they conclude that the following articles are practically free from nuclein causing uric acid elimination: milk, cheese, eggs, white bread, butter, rice, lettuce, cabbage and potatoes. Such a diet they call a "purin-free diet." They consider that the uric acid eliminated by an individual on a purin-free diet is derived exclusively from endogenous sources. They have also attempted to analyze accurately articles of food rich in nucleins that produce purin elimination. Such foods are thymus, liver, pancreas, spleen, kidney, and among the vegetables, peas and beans. The extractives from muscle also contain nuclein.

It has been contended by Burian and Schur and others that the endogenous uric acid normally eliminated by man on a purin-free diet is a constant quantity for each individual, but that this may vary in different individuals. In one individual the value of the daily endogenous uric acid elimination was found not to vary more than 0.03 grams in determinations made at different times in a period of 18 months. In different individuals it varied from 0.2 grams to 0.7 grams. It is stated that this constant value represents the minimum amount of uric acid excreted by the individual; that the constant figure indicates normal metabolism; that its increase points to increased cell destruction going on in the body. The statements in this paragraph apply only to uric acid metabolism in health.

From experiments the conclusion has been drawn that it is also possible, when a person is on a mixed diet, to determine what portion of the uric acid elimination is endogenous and what portion is exogenous. The degree to which the foods rich in nuclein and preformed purins cause uric acid elimination is said to depend not on the individual, but on the amount and kind of food ingested. For example, it is claimed by Burian and Schur that about 50% of the amount of uric acid or other oxypurins taken into the body with the food under normal conditions is constantly eliminated as uric acid, and that while the remaining 50% may undergo further decomposition in the course of metabolism, being changed into other products, this certain definite portion is eliminated unchanged. This would give a method for determining the exogenous portion of the uric acid elimination, providing the nuclein content of different foods could be accurately estimated. If the metabolism of exogenous and endogenous uric acid were carried on in the same way and in accordance with this law, the endogenous uric acid eliminated in the urine would represent 50% of that normally formed by the metabolic processes of the body independently of the food. Variations from these proportions would show that the metabolism was not normal and the degree to which the body could eliminate, as uric acid, the purin bases taken with the food would indicate the degree to which it could oxidize the uric acid arising in itself.

These views regarding uric acid metabolism in health are largely the result of the experimental studies of Burian and Schur, and Siven and have been somewhat widely accepted. They have also been made the basis of some few studies with regard to uric acid metabolism in disease, and especially in gout. The studies of Vogt and others[8] lead them to the conclusion that in gout the exogenous purins are more slowly excreted than in health. Kaufmann and Mohr[9] have published studies which indicate that the values of both endogenous and exogenous uric acid between attacks are within normal limits. It is generally admitted that in the acute gouty attack there is constantly a greater excretion of uric acid than in the free intervals, and that probably it is preceded by diminution. When attacks follow each other irregularly the picture becomes confused. There has been considerable discussion as to whether the curves of the uric acid and of the phosphoric acid excretion are parallel in gout, but the matter cannot be said to be entirely settled.

The present investigation was undertaken for the purpose of obtaining, if possible, further information on these points.

The case here reported is one of chronic gout in which a few urinary tests were made while the patient was on a purin-free diet. The first series of analyses cover a period of 10 days. The 24-hour quantity, the specific gravity, and the daily amount of uric acid and of phosphates were determined.

The uric acid was determined by the Folin-Hopkins method, and the phosphoric acid by titration with uranium nitrate. The conditions under which the patient lived were constant as regards exercise (which consisted of light work about the ward) and sleep. Movements of the bowels occurred regularly. The urine was collected and kept in a large stoppered bottle in the bathroom of the ward until the 24-hour amount was obtained, and then placed on ice. The room temperature varied from 72° F. to 85° F.

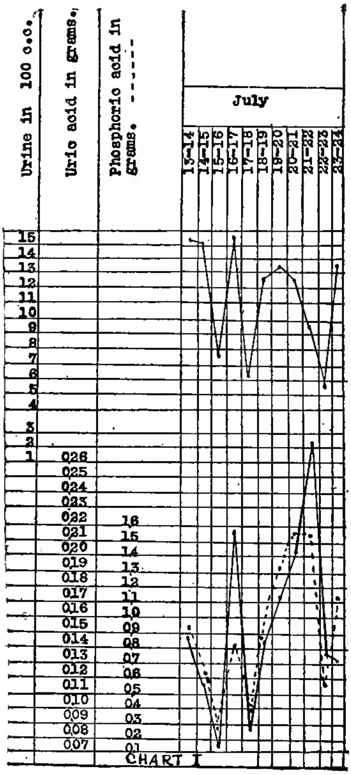


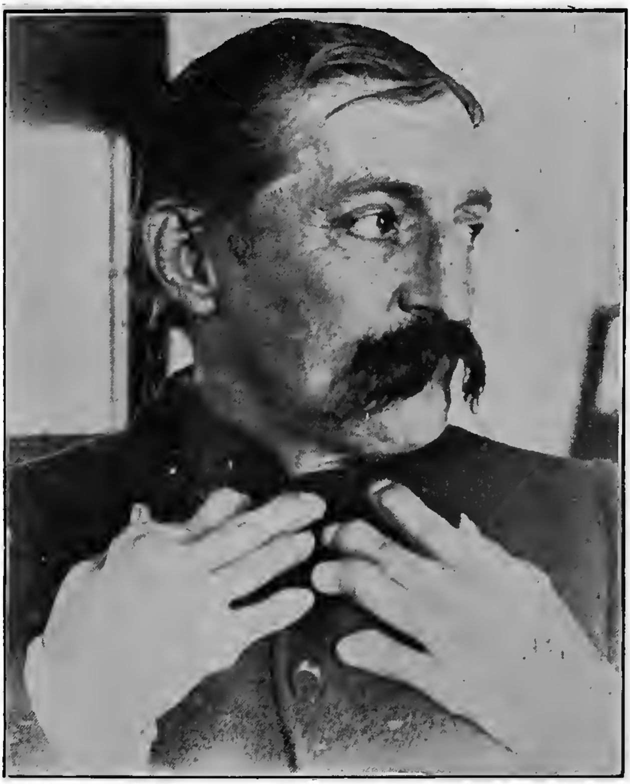
CHART I

Case.—C. F., male, aged 52, gardener and storekeeper, American, was admitted to the Albany County Hospital, October 23, 1902, complaining of swollen joints of hands and feet. His father was born in England, used alcohol freely; mother still living, born in this country of English parents. Her people used liquors freely. There is no family history of gout or rheumatism.

The patient has used alcohol all his life. Ale has been his favorite beverage. He has always eaten freely, especially of meats and sweets. He has never been compelled to do much hard work. The first attack of gout affecting the great toe of the right foot, occurred about 12 years before his admission to the hospital. Since then he has had recurring

To Illustrate Dr. Laird's Article on "The Elimination of Endogenous Uric Acid in a Case of Chronic Gout"

Albany Medical Annals, November, 1905



similar attacks in various joints. The joints of the fingers and toes have repeatedly become swollen and now tophi may be seen in the fingers, toes, heels, in both ears, and on the nose. Physical examination of the chest is negative as regards the lungs; the heart is enlarged and aortic murmurs, both systolic and diastolic, are heard. The urine contains a trace of albumin, and a few hyaline and granular casts, but no sugar. Clinical determinations of urea by the Doremus method give uniform low values, 8 grams to 26 grams per day. Leukocyte count July 15, before dinner, 6,000.

The tests were commenced July 13, 1904. At first the diet was not modified, and consisted of oatmeal and milk for breakfast; tea, bread, and vegetables for dinner, and bread and tea for supper. As the patient ate no meat, it was practically a purin-free diet. July 19 he was put on the following purin-free diet: breakfast consisted of white bread and milk, with an egg; dinner was the same as breakfast; supper consisted of bread and milk.

TABLE I.

Date. 1904.	Urine in cc.	Specific gravity.	Uric acid in grams.	Phosphoric acid in grams.	Remarks.
July 13–14...	1520	1010	0.149	0.912	Patient feeling well; temperature normal; about ward.
" 14–15...	1505	1011	0.116	0.622	
" 15–16...	770	1010	0.075	0.269	
" 16–17...	1540	1010	0.219	0.800	No marked pains.
" 17–18...	620	1010	0.087	0.372	
" 18–19...	1265	1009	0.142	0.875	
" 19–20...	1335	1010	0.173	1.33	
" 20–21...	1260	1010	0.205	1.575	Severe pains in several joints; temperature, 100.6°.
" 21–22...	970	1010	0.271	1.57	Patient in bed.
" 22–23...	550	1011	0.138	0.583	Feeling better today.
" 23–24...	1335	1012	0.132	1.140	Feeling well; out of bed.

The patient was about the ward and able to help in light work, though suffering some slight pain, until the early morning of July 21 (2 a.m.), when he began to have severe pains in the fingers, shoulders, and hips. His temperature, which had previously been normal, rose to 100.6° at 7 a.m. He remained in bed during the day, and by night the pains had become less severe. On the morning of July 22 the house physician prescribed wine of colchicum, of which the patient received 18 drops on July 22, and also the same amount on July 23 and 24. On July 24 he was out of bed.

Table I and Chart I give the total amount of urine in 24 hours, the specific gravity, uric acid, and phosphoric acid.

The second series of analysis covered a period of about 22 days. On four days (August 25, 26, 27, and September 3) no tests could be made. The urine was collected in stoppered bottles and put, as soon as passed, on ice, in a small refrigerator placed in the ward for that purpose, and it remained on ice until the tests were made. (The fact that the urine was placed on ice at once without waiting until after the 24-hour amount was collected makes the results in the second series of tests somewhat more accurate than those in the first.) A record was kept of the temperature, pulse, respiration, and number of stools. Frequent leukocyte counts were made. The 24-hour amount of the urine, the specific gravity, and the daily excretion of uric acid and phosphoric acid were estimated, the same methods being used as in the first series. A number of determinations of the total acidity of the urine was also made. Both the Freund and the Folin methods were used in parallel tests. The room temperature varied from 70° F. to 83° F.

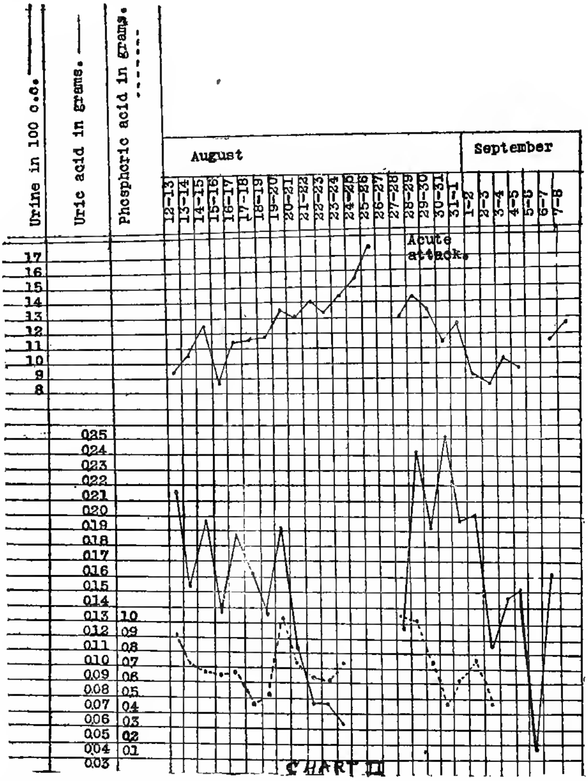


CHART III

During this series of tests the patient was kept on the following diet: Breakfast, an egg, soft boiled, with bread and butter and glass of milk. Dinner, same as breakfast. Supper, a bowl of bread and milk. The only modifications were: August 27, he ate no eggs; August 31, the egg was omitted at breakfast; September 1, breakfast consisted of a slice of bread and butter; September 2, no eggs were eaten. Water was allowed, but the patient drank little of it (except on August 28, when he drank six glasses); on August 30 and 31 he did not take any water.

With regard to exercise and bodily exertion, the patient walked about the ward and helped in light work, such as washing dishes and making beds.

He was quite free from pain until August 19, when one of the joints of the right forefinger became painfully swollen, and August 20, the skin ruptured, and a discharge of whitish puriform material occurred. He had little pain from that time until August 29. August 29, 6 a.m., the left heel became swollen and painful. August 30, patient in bed. The skin over the heel broke, and a profuse bloody discharge containing white particles occurred, which gave marked relief. At this time there was pain on swallowing, pain and soreness in the neck and about the clavicles, with more or less pain throughout the entire left side. Hot lead water and laudanum were applied the painful areas. At 5 p.m. the temperature was 100.2°. August 31, the pain and stiffness were much less marked. September 1, some headache and stiffness about the back of the neck. September 2, pains all over the body. September 3, pains had disappeared, and patient felt better. September 4, patient out of bed. No medicine was given during this series of tests.

TABLE II.

Date.	Urine in cc.	Specific gravity.	Uric acid in grams.	Phosphoric acid in grams.	Remarks.
August 12–13.	985	1015	0.216	0.908	No marked pains.
“ 13–14.	1030	1010	0.154	0.715	
“ 14–15.	1230	1010	0.196	0.682	
“ 15–16.	890	1012	0.138	0.649	
“ 16–17.	1140	1015	0.188	0.684	
“ 17–18.	1180	1014	0.161	0.483	
“ 18–19.	1190	1012	0.138	0.505	Joint of forefinger swollen.
“ 19–20.	1350	1014	0.192	1.026	Discharge from forefinger.
“ 20–21.	1300	1015	0.112	0.728	Comparatively free from pain.
“ 21–22.	1400	1014	0.079	0.63	
“ 22–23.	1320	1011	0.076	0.60	
“ 23–24.	1420	1011	0.063	0.724	
“ 24–25.	1550	......	......	......	
“ 25–26.	1750	......	......	......	
“ 26–27.	......	......	......	......	
“ 27–28.	1300	1011	0.126	1.059	
“ 28–29.	1420	1010	0.231	1.022	Left heel swollen; painful.
“ 29–30.	1350	1011	0.192	0.735	Heel discharging freely.
“ 30–31.	1150	1011	0.250	0.493	....
September 1–2	1280	1011	0.196	0.62	Pain less marked.
“ 2–3	930	1011	0.202	0.781	....
“ 3–4	1010	1012	0.111	0.484	No pains.
“ 4–5	980	1012	0.147	......	Patient out of bed.
“ 5–6	......	......	0.152	......	....
“ 6–7	1150	......	0.046	......	....
“ 7–8	1260	......	0.160	......	....
“ 8–9	1525	......	......	......	....

Table II and Chart II give the amount of urine in 24 hours, the specific gravity, and daily excretion of uric acid and phosphoric acid.

Table III—the temperature, pulse, respiration, stools, and leukocyte counts.
Table IV—the determinations of the total acidity of the urine.

Daily microscopic examinations of the urine showed constantly a trace of albumin, and a few hyaline and granular casts. Clinical urea determinations by the Doremus method gave low values—17 grams to 20 grams per day.

It will be noted from a study of the tables and charts that the *"endogenous"* uric acid elimination was, for the most part, below that of a normal individual. According to the investigations quoted, the extremes in daily excretion in different normal individuals were 0.2 grams and 0.7 grams. In this case the daily excretion was always below 0.2 grams, except at the time of acute exacerbations, when the highest point reached was 0.27 grams. The lowest point reached was 0.046 grams. Between these two extremes were marked fluctuations. The values in the intervals between acute exacerbations were not invariably low, but on several occasions approached the highest values reached during an attack. Kaufmann and Mohr[9] found the endogenous uric acid excretion in five cases of chronic gout to be within

TABLE III.

Date	Hour.[1]	Temperature.	Pulse.	Respiration.	Stools.	Leukocytes.	
						Hour.	Number per cm.
August 12–13.	10.30 a.m.	98	72	24	0	....	....
" 13–14.	9.20 a.m.	97	80	25	0	....	....
" 14–15.	11.15 a.m.	97.2	80	16	1	11.15 a.m.	9,000
" 15–16.	10.15 a.m.	97.6	72	24	1	4.30 p.m.	7,000
" 16–17.	3.30 p.m.	97.6	72	20	1	3.30 p.m.	7,000
" 17–18.	9.30 a.m.	97.6	72	20	1	9.30 a.m.	6,000
" 18–19.	2.30 p.m.	97.8	80	18	1	....	....
" 19–20.	5.30 p.m.	98.8	68	30	1	5.30 p.m.	6,400
" 20–21.	2.30 p.m.	98	72	20	1	....	....
" 21–22.	3 p.m.	98.8	64	24	1	3 p.m.	5,200
" 22–23.	6.15 p.m.	98.4	68	20	1	6.15 p.m.	5,200
" 23–24.	3.15 p.m.	98.4	68	20	1	3.15 p.m.	6,440
" 24–25.	4 p.m.	98	72	18	1	....	....
" 25–26.	9 p.m.	99.6	72	18	1	....	....
" 26–27.	2.30 p.m.	98	64	20	1	2.30 p.m.	6,060
" 27–28.	8.30 a.m.	98	84	20	1	8.30 a.m.	6,000
" 28–29.	11 a.m.	98.8	84	20	1	11 a. m.	6,000
" 29–30.	9.30 a.m.	98	72	20	1	....	....
" 30–31.	5 p.m.	100.2	72	20	1	5 p.m.	7,000
" 31–1..	9.30 a.m.	98	72	20	1	....	....
September 1–2	11 a.m.	97	72	16	1	11 a.m.	7,000
" 3–4	9 a.m.	98	72	....	1	....	....
" 4–5	....	99	80	18	1	....	....

normal limits, varying between 0.357 grams and 0.660 grams per day in different cases. One of Futcher's[10] patients, during three periods of twenty-four hours each, had practically no uric acid excretion.

In a general way in the first series, the phosphoric acid curve follows the uric acid curve, as closely, certainly, as in Cases II and III, reported by Futcher.[10] It will be noted, however, that in the second series of tests, between August 27 and 31, the phosphoric acid curve fell, while the uric acid curve was rising to its highest point. This recalls Futcher's statement in regard to his Case III: "There was, however, an unexplainable drop in the phosphoric acid curve between April 8 and 17, when it failed to correspond at all with the uric acid curve." In the paper referred to there is no statement indicating that the patient was kept on a purin-free diet. It will be noted that the daily excretion of phosphoric acid in this case is considerably below the normal given by Futcher (2.5 grams); the highest point reached in our determinations being 1.57.

TABLE IV.—ACIDITY.

Date.	Cc. of uranium solution used for 50cc. urine.	Freund method.		Cc. of N/10 NaOH per 25 cc. urine.	Folin method.	
		Corresponding number of cc. of N/10 NaOH per 100 cc. urine.	Cc. of N/10 NaOH per 24 hours.		Cc. of N/10 NaOH per 100 cc. urine.	Cc. of N/10 NaOH per 24 hours.
August 17–18.	1.35	3.69	43.54	2.8	11.2	132.16
" 18–19.	1.2	3.27	38.91	2.9	11.6	138.04
" 19–20.	2.1	5.71	77.08	3.95	15.8	213.30
" 20–21.	1.2	3.27	42.51	5.87	23.58	307.54
" 21–22.	1.55	4.23	59.22	5.95	23.8	333.20
" 22–23.	1.2	3.27	43.16	5.1	20.4	269.28
" 23–24.	1.15	3.17	45.01	5.15	20.6	288.85
" 24–25.	....	....	....	....	....	....
" 25–26.	....	....	....	....	....	....
" 26–27.	....	....	....	....	....	....
" 27–28.	2.65	7.24	94.12	7.67	30.68	398.84
" 28–29.	2.5	6.83	96.98	6.6	26.4	374.88
" 29–30.	2	5.46	73.71	5.15	20.6	278.10
" 30–31.	1.2	3.27	37.60	4.85	19.4	223.10
" 31–1..	1	2.73	34.94	5.3	20.52	262.71
September 1–2	1.47	4.01	51.32	7.7	28.8	257.84
" 2–3	....	....	....	....	....	....

The leukocyte counts made at irregular intervals in connection with the second series of tests do not suggest any definite relationship between the number of leukocytes and either the phosphoric acid or uric acid excretion. No constant digestive leukocytosis was noted, and the count was always distinctly within normal limits.

The total acidity was determined both by the Freund[11] method (which is based upon the assumption that the acid reaction of the urine is referable exclusively to the diacid phosphates) and by the Folin[12] method. Folin believes that the Freund and all similar methods are open to the fatal objection that a considerable part of the acidity of the urine is due to organic acids. He titrates the urine with decinormal sodium hydrate solution after first guarding against the disturbing effect of calcium and ammonium salts by the addition of about 20 grams of powdered potassium oxalate to the 25 cubic centimeters of urine titrated.

In this series of tests the Folin method gave uniformly higher values than the Freund method. Even the determinations by the Folin method were below the normal values given by Folin[13] as varying, in thirty normal urines, between 554 cubic centimeters and 669 cubic centimeters of decinormal sodium hydrate solution per twenty-four hours, and below values he obtained for individuals on a similar purin-free diet. The highest value obtained in this series was 398 and was found on August 28. It was nearly as high on August 29. These were the days when the patient was suffering more pain than usual. No constant relationship appears to exist between the total acidity and the excretion of uric acid in this case.

Definite conclusions regarding uric acid formation cannot be drawn from such experiments as are here reported. While it has been considered justifiable to make important deductions regarding uric acid formation in health from a study of uric acid excretion, the presence of disease conditions introduces disturbing factors. The recent work of Löwi,[14] Folin[15] and others, indicates that even the widely accepted theories of Burian and Schur regarding uric acid metabolism in health may not be well founded. Löwi claims that it is impossible by our present methods to determine accurately the amount of exogenous or endogenous purin eliminated. Folin[15] has found the endogenous uric acid elimination in health not to be constant on certain purin-free diets. He questions whether all the endogenous uric acid eliminated in health is derived from the nuclein of body cells. The possibility of the synthetic formation of endogenous uric acid in man, even in health, is asserted by several investigators.[16] If it were true, as has been claimed by Burian and Schur, that in health the uric acid eliminated in the urine represented half of that formed in the body, and this proportion remained constant in disease, quantitative uric acid determinations would certainly be of great value. Other factors in metabolism, such as digestion, sleep and exercise, would, however, still have to be considered. Digestion affects uric acid elimination decidedly, if constipation or diarrhea occur. According to Schittlhelm,[17] the purin bodies found in feces are in part derived from unabsorbed parts of the food, in part from bacteria, and in part from the secretion of intestinal glands. In diarrhea, a rapid passage of food purins through the intestine would increase the fecal output, and less purin would be absorbed to be excreted in the urine. In this case there was no diarrhea, the bowels moving regularly, as noted in Table III. Siven,[18] Pfeil and Rockwood have found the elimination of uric acid to be greater by day than by night; Rockwell suggests that the difference is due to a lessened rate of cellular metabolism during rest in bed. Sherman[19] has failed to find any increase in uric acid elimination resulting from vigorous exercise. Rockwood[18] found an increase in endogenous uric acid elimination after exhaustive labor, but not after moderate exercise. It has been maintained[20] that if the subject is in poor physical training, exercise causes an increase in uric acid elimination. It is probable that there was chronic nephritis in this case; this introduces another disturbing factor.

Whether there is really a constant relationship between the endogenous uric acid elimination and the "endogenous" phosphoric acid elimination in this case, cannot be inferred, since the diet, while purin-free, was not free from elements containing exogenous phosphoric acid. Phosphorous may be taken into the food in other forms than that contained in the nucleins, and according to Chalmers Watson [21] and others, this prevents any possible parallelism in the curves. Kauffmann and Mohr [22] state that phosphoric acid excretion varies with the varying needs of the body for phosphoric acid.

Horbaczewski's theory that endogenous uric acid was derived exclusively from the breaking down of leukocytes is no longer accepted. The work of Magnus-Levy,[23] Richter,[24] and others, has demonstrated the fallacies of his arguments and there does not now seem to be any reason why the leukocyte curves should parallel the uric acid curve. There is no constant parallelism between the two in this case.

SUMMARY.

The uric acid elimination in a case of chronic gout kept on a "purin-free" diet was below so-called normal limits. In the intervals between the exacerbations there was marked variation in the amount of uric acid eliminated. Low values were reached preceding acute symptoms, and at times during the intervals the excretion was very low, at other times, however, the highest values reached during an attack were approached.

The phosphoric acid elimination was below normal. In the first series of tests the phosphoric acid curve followed the uric acid curve quite closely; in the second series, not at all.

The leukocyte counts were normal. They did not vary with the uric acid excretion. No digestive leukocytosis was noted.

The acidity was at all times below the average normal acidity. The highest values were obtained during one of the acute exacerbations.

Present views regarding uric acid elimination may be summed up in a few words: The principal source of the uric acid eliminated by man under normal conditions is the nucleins. We find an increased elimination of uric acid following the ingestion of substances contained nucleins. This source of uric acid can be controlled. The endogenous uric acid is probably derived from more than one source. A large portion comes from the decomposition of the nuclein of body cells, but a part is probably formed by direct synthesis. When certain purin-free diets have been used, the endogenous uric acid has in certain individuals shown a somewhat constant value in health, when other factors in metabolism were constant. When other forms of purin-free diet were employed the amount of endogenous uric acid was not constant, even in health. In disease the elimination of uric acid has shown marked fluctuations. How large a portion of the endogenous uric acid elimination under pathologic conditions is formed by synthesis is not known. The nucleins are one source of the phosphoric acid excretion in the urine, but not the only source, and there is no constant relationship between uric acid and phosphoric acid excretion.

Though the leukocytes are a source of endogenous uric acid they are by no means the only source, and their number has no constant relationship to the excretion of uric acid. The work of the past few years has shown the fallacies in certain generally accepted theories regarding the source of uric acid and established definitely a very few facts in regard to uric acid metabolism. The part which uric acid plays in gout is still unsettled.

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MALIGNANT OVARIAN TUMORS IN CHILDREN; WITH REPORT OF A CASE.

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The following case of a malignant ovarian cyst in a girl thirteen years old, emphasizes some of the clinical features of this unusual condition and on this account seems worthy of reporting in full.

History of the Case.

Miss C. P., a schoolgirl, aged 13, was admitted to the service of Dr. Willis G. Macdonald, at the Albany City Hospital, October 20, 1904, complaining of severe abdominal pain.

Family History.—Father, mother and two sisters living and well; two great aunts and one aunt and one uncle on father's side said to have had cancer.

Past History.—Very healthy child; no sickness before present illness; menstruated for the first time on September 3, 1904; flowed five days and menstruation was apparently normal. Leucorrhoea present during last few months.

Present Illness.—On the afternoon of September 11th, menstruation having ceased, she was taken with severe colicky pains in abdomen, which radiated into the shoulder. These pains soon disappeared and she became quiet until about 10 p. m., when she was again seized with an attack of a similar character. At the end of 24 hours she felt well, and remained so for three weeks, when she had a third attack similar to the previous ones. Since the onset of this last illness (on the 11th of October) she has been incapacitated, owing to the frequent and severe attacks of pain. For the past few days she has had fever (102° and over) and has been vomiting.

Clinical Diagnosis.—Ovarian cyst (ruptured) with twisted pedicle.

Operation.—A median incision exposed the peritoneum through which could be seen haemorrhagic material in the abdominal cavity. On opening the latter, it was seen to be filled with free and clotted blood. Further examination revealed an ovarian cyst which had ruptured. The blood was wiped out of the peritoneal cavity and after ligating the pedicle of the cyst, it was removed. A glass tube was inserted and the abdominal incision closed with silkworm gut. The patient was discharged November 12, 1904.

She was admitted to the service of Dr. Macdonald again on November 29, 1904, and gave the following history. About five days after the patient left the hospital she complained of soreness and pain in the right side which was soon followed by an attack of sharp pain lasting from one afternoon until the next morning. She has had numerous other attacks since, the pain extending chiefly down the right leg. Her appetite has been poor and vomiting has been more or less constant.

Her bowels have moved three or four times daily; stools have been pencil shaped; no bloody stools noted. She has lost weight and is very anaemic. For the last three days the patient has been kept in bed, on a strict liquid diet. Temperature for the last two or three days has been at least as high as 100.7°. A swelling on the right side of the abdomen was noticed before coming to the hospital.

An exploratory operation was performed on the 29th of November. An incision was made over the tumor, which was situated on the right side just below the liver. On opening the abdominal cavity a bloody fluid, in which were found pieces of grayish tissue, escaped. The cavity was thoroughly irrigated and a drainage tube, flanked with strips of iodoform gauze, was inserted. The patient lived for nearly a month after the operation, but finally became delirious and restless, refused food, and died on December 20, 1904. An autopsy was made by Dr. E. MacD. Stanton, from whose notes the following descriptions have been taken.

Anatomical Diagnosis.—General sarcomatosis of abdominal cavity. Extreme secondary anaemia. Thrombus in right heart. Operation scars on abdomen.

Abdominal Cavity.—The entire left side of the abdomen and pelvis is filled by a tumor mass which reaches to the anterior abdominal wall and is for the most part covered by a portion of the omentum. The left border of this mass extends from a point 5 cm. to the left of the symphysis pubis upward to the under border of the liver at a point 5 cm. to right of the median line. The coils of intestine adjacent to the tumor mass are loosely adherent to one another by easily torn adhesions which are apparently, for the most part, composed of the tumor itself. The remainder of the abdominal cavity contains a few cubic centimetres of bloody fluid. The peritoneal surfaces show a slight loss of lustre, with here and there, small tumors adherent to the peritoneum. These smaller masses vary from a few millimetres to 4 or 5 centimetres in diameter. Their surfaces are smooth with a thin peritoneum-like covering. Two of these masses situated on the under surface of the diaphragm have caused corresponding depressions in the right lobe of the liver. The head of the caecum and appendix together with the pelvic organs are imbedded in the new growth. The ascending colon and small intestines have been pushed over the left border of the tumor.

The general structure of the large and smaller tumors is similar. The free surface of the larger tumor is somewhat lobulated and of a mottled grayish and dark red color. The cut surface of the firmer portions of the tumor is also mottled grayish yellow and dark red, the red areas representing areas of hemorrhage into a soft succulent, grayish-yellow tissue which in many places is necrotic. The entire center of the larger mass is occupied by an ill-defined area of softening which is filled with partially clotted blood and fragments of necrotic tumor tissue. The tumors do not infiltrate the tissue beneath the peritoneum, it being possible in the case of the larger tumor to strip the parietal peritoneum from the abdominal wall.

Pelvic Organs.—All pelvic structures are imbedded in the soft tumor mass described above. The left tube and ovary, the body of the uterus, the rectum and the bladder are negative except for the presence of tumor metastases or implantations on their peritoneal surfaces. The right ovary is missing, together with all but the proximal 3.5 cm. of the right tube. On the stump of the right tube are seen several silk ligatures which show almost no evidence of encapsulation.

Liver.—Weight, 1560 grammes. The upper surface of the right lobe shows several depressions, the two larger of which measure respectively 2 and 5 cm. in diameter. These depressions are caused by two tumor masses which are adherent to the under surface of diaphragm. The under surface of the right lobe of the liver is in contact with a shaggy grayish-yellow blood stained mass representing the upper and of the large tumor mass described above. Adherent to the under surface of the left lobe of the liver is another tumor mass 2.5 cm. in diameter. On section the liver presents a pale brownish yellow surface with indistinct markings.

Gastro-intestinal Tract.—Appendix measures 15 cm. in length and is imbedded in the tumor mass. The remainder of the gastro-intestinal tract is negative, except for the presence of small new growths scattered here and there over its peritoneal surface.

Pleural cavities, pericardial cavity, heart, spleen, kidneys, adrenals, pancreas, vagina and external genitals and cavity of the uterus are all negative.

Gross and Microscopic Appearances.—The specimen removed at the first operation was described by Dr. Stanton as being a large, mutilated, haemorrhagic and necrotic ruptured unilocular ovarian cyst. Its surface was fairly smooth though in a few areas could be felt fine hard granules, and its lining membrane was covered with intimately adherent blood clots.

On microscopic examination isolated groups of cells suggesting cancer were found, but these were stained so poorly, owing to the necrosis of the cyst wall, that a positive diagnosis as to their character could not be made.

The tissue removed at the second operation, on November 27th, and examined by Dr. Stanton, consisted of a few fragments of blood stained material. The anatomical diagnosis was then made of "multiple malignant growths due to implantation from a ruptured ovarian cyst." Microscopic examination of these tissues showed a highly cellular stroma composed of numerous spindle and round cells of both the large and small type. These large spindle and round cells constituted the predominating cells of the stroma. Distributed here and there in this tissue were numerous masses of epithelial cells arranged in "irregular gland-like tubules." This cellular arrangement led to the microscopic diagnosis of "so-called adeno-sarcoma."

Sections of the tumor growth removed at autopsy show a highly vascular tissue, many of the blood vessels of which are definitely formed and distinctly show the three vascular coats. Here and there are large areas of necrosis and haemorrhage about which are strands of a well formed granulation tissue. The histologic picture is somewhat intricate, inasmuch as in different sections the character and arrangement of the cells vary. In all, however, a very noticeable element is the rambling stroma, in the meshes of which are various types of cells, some resembling the spindle and round cells of sarcoma, others distinctly epithelioid, and still others with syncytial arrangement and again cells of definite epithelial or endothelial type. The latter are often arranged in gland-like tubules.

Examination of the smaller peritoneal nodules reveals practically the same picture as that found in the main tumor mass, namely, a stroma of spindle and round cells with masses of epithelium arranged in gland-like fashion. One section, however, taken from a nodule attached to the peritoneum by a slight and slender pedicle, presents an interesting picture of a well formed cyst. The wall of this cyst is composed of masses of spindle cells arranged as in sarcoma while the cavity is lined by columnar epithelium. This section resembles closely the new growth known as cystic adeno-sarcoma.

From the histological picture of the main tumor growth as well as that of the smaller nodules, it is evident that a microscopical diagnosis is very difficult. Owing to the peculiar arrangement of the epithelium scattered throughout the growth, one is tempted to consider the tumor as an adeno-carcinoma. On the other hand, however, the appearance of the stroma, which seems to be an intermediary type between newly formed connective tissue and true ovarian stroma containing as it does a vast number of spindle and round cells almost entirely devoid of intercellular substance, suggests a sarcomatous growth. Indeed, many malignant growths of the ovary present such peculiarities in their structure that various terms have been applied to them in attempts to combine the sarcomatous, the carcinomatous and the cystic characteristics in a single name applicable to all. Thus we have the terms adeno-carcinoma, adeno-sarcoma, cystic adeno-sarcoma, cystic endothelioma, sarco-endothelioma and Leopold's endothelioma lymphaticum and endothelioma vascularis. Poupinal speaks of secondary tumors as being of the sarco-carcinomatous type, although he does not state that the primary growth also may be a mixed tumor. Echardt and Pomorski have used simply the term " endothelioma of the ovary."

When such a number of terms are applied to these mixed tumors, how are we to histologically differentiate between them, and are we always justified in allowing a diagnosis to rest on a few sections? Kelly points out that " a thorough sifting of material from ovarian tumors, in the pathological laboratory, has served to demonstrate the necessity of a careful microsocopical examination in every case;" and so an attempt has been made to examine most carefully the tumor which is here reported. The result, however, has been unsatisfactory and no definite conclusion has been reached. Adena-carcinoma or "adeno-sarcoma" seems to be the most plausible term to apply in this instance, but each has objections. We must be satisfied therefore in describing it, as a malignant ovarian tumor, the stroma of which resembles ovarian stroma and in places suggests a sarcomatous structure, while scattered throughout it are masses of cells having the arrangement of an adeno-carcinoma.

The history of this case brings out sharply the following points:

1 Ovarian cysts may occur in children and may be malignant.

2 The pedicle may become twisted and as a result give rise to severe abdominal pain, thus leading to a diagnosis of the cyst.

3 The rupture of the cyst and the distribution of its contents throughout the peritoneal cavity may lead to a general implantation of the growth and soon cause death.

4 The histological diagnosis of these cases is frequently difficult.

Little is said in either the text-books or the general literature concerning malignant ovarian growths in children. My interest in the case here reported has prompted me to examine the histories of the various cases heretofore reported in regard to the following points.

1 What are the principal malignant ovarian tumors in children?

2 What is the relative frequency of these tumors?

3 Do malignant ovarian tumors present any clinical manifestations different from those presented by the benign growths?

4 How frequently do accidental conditions such as twisting of the pedicle or rupture of the cyst give the first warning of the presence of an ovarian growth?

5 Are seemingly benign growths of the ovary to be looked upon as harmless, as are benign growths of other organs.

Unfortunately, I have not been able to obtain much information, for the references are few, and, in the majority of the cases, meagre in clinical data.

The cases of ovarian tumors which have been reported as occurring in children, embrace a number of types of new growths, which may conveniently be divided into the benign cysts, sarcoma and carcinoma; and in addition to these, a fourth type, the mixed tumor, which, owing to the difficulties attending the determination of its structure and histogenesis, affords scope for argument as to its classification.

The benign cysts may be divided into the dermoid, and the simple uni- and multilocular cysts. The sarcomata are usually of the round or spindle cell types; while the adeno-carcinoma seems to be the most prevalent type of the epithelial tumors. The mixed tumors have been discussed in the first part of this report.

It is impossible to arrive at conclusions regarding the benignancy or malignancy of new growths of the ovary reported in the literature as "cysts." The fact that they are thus reported does not in the least confirm the idea that all are benign. Our own case shows the possibilities of malignancy in an apparently simple cyst.

Upon careful review I have been able to collect seventy-two cases of malignant tumors occurring in girls between the ages of twenty-two months and fifteen years. The relative frequency of the malignant tumors as compared with the benign growths of the ovary in children is comparatively small. Whether this is due to the fact that histological study has been neglected in a number of cases, or whether perhaps, the very small areas of the cyst wall which contain the malignant cells have escaped the examiner's notice, or whether cases have been reported too soon after the operation, thus affording little time for the observance of recurrence or whether surgeons have failed to report cases which have ended fatally, it is not my purpose in this report to state although these various possibilities have occurred to me during this study of the literature.

The fact however remains that malignant tumors of the ovary do occur in young children, and it is therefore the duty of the physician and the surgeon to look upon all ovarian growths as possessing possibilities of malignancy.

A study of the reports of malignant ovarian tumors here collected reveals the fact that clinically it is impossible at first to distinguish the benign cyst or tumor from a malignant growth.

The symptoms of the two conditions may be identical and to this fact is due the difficulty of differentiating between the two forms. Both may develop slowly and without causing the patient pain, as the latter seldom is present unless a twist of the pedicle or some other complication occurs. As the tumor grows, however, symptoms referable to a malignant growth may follow, such as emaciation and those arising from metastasis or implantation. The histories present little variation since the health of the individual, in the majority of the cases, has been reported as "good" up to the third, fourth, fifth or sixth month before the detection of the new growth.

Symptoms calling attention to the tumor vary.

1 Some cases were discovered accidentally in operating on other organs.

2 In others, symptoms referable to an abdominal tumor, such as tightness of the clothing, dyspnoea, or constipation, have led to the diagnosis.

3 In some cases the patient came under observation on account of pain.

4 In a few cases the patient was examined on account of an associated bloody vaginal discharge.

5 Symptoms of an acute abdominal condition arising from twisting of the pedicle or rupture of the tumor, indicated the proper diagnosis in several instances.

In some of the cases here tabulated, the diagnosis of sarcoma of the kidney, hyatid of the liver, tuberculous peritonitis, sarcoma of the spine, hæmatocele, hydronephrosis or typhoid fever was made. An astonishingly small percentage of the diagnoses were correct, showing beyond a doubt that the condition when it does occur in children is not readily recognized owing either to the difficulty of interpreting the symptoms or to the infrequency of the disease.

The occurrence of malignant ovarian cysts in children and the impossibility of differentiating them from benign cysts before metastases or implantations occur emphasizes the importance of an early diagnosis and operation in all cases. The case reported in this article supports this statement as does also the experience of the following investigators. De Senety states that "it seems impossible to draw a line of demarcation between ovarian cysts and ovarian cancers;" Kelly says that "from a practical standpoint all ovarian tumors must be considered as malignant until removed and proved otherwise." Pozzi remarks that "it is much better to always take the worst view of the case and always to fear generalization." Hofmeier and Cohn have, too, layed much stress on the fact that "glandular cysts may present cancerous degeneration," and Leopold fearing this degeneration has given it as a general rule that every ovarian tumor should be removed as soon as it is recognized. Bland Sutton quotes Jessup who once reported a case in which a ruptured dermoid cyst metastasized to the liver, the suprarenal capsule and the mesenteric glands.

As regards the frequency of the disease at the different periods of early life, the cases which I have tabulated reveal the fact that 60 per cent. occur between the age of ten and fifteen, while the cases ranging from birth to five years form but about 14 per cent. of the total number.

Two tumors simply reported as malignant ovarian tumors have not been included in the tables given below nor are the four carcinomata reported in Keating's Encyclopædia of Diseases of Children (p. 739) since the records contains no reference to age.

Table I—Type of Tumor According to Age.*

	Birth to 5 yrs.	5-9 yrs. incl.	10-15 yrs. incl.	Per cent.
Carcinoma	1	6	19	40
Sarcoma	8	10	18	55.4
Endothelioma	0	1	2	4.6
	13.8%	26.2%	60%	

In the table below the result of the operation has purposely been omitted inasmuch as the majority of the reports did not state whether the patient died as the result of operation, or as the result of the occurrence of metastases; also in those given as recoveries it was impossible always to determine the length of time after operation.

CONCLUSIONS.

1 Malignant ovarian tumors may occur in children.

2 In the first stages of the disease the clinical symptoms of the benign and malignant tumors are identical.

3 The tumor may be discovered accidentally or from symptoms arising from a rupture of the cyst or a twisting of its pedicle, which may be the first evidence of the presence of an ovarian tumor.

4 Children of all ages are susceptible to the disease although it occurs most frequently in children between ten and fourteen years.

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* The figures here given cannot be regarded as conclusive for in many cases no microscopic examination was made.

5 All ovarian tumors should be regarded with suspicion because of the possibilities of malignancy.

6 Rupture of ovarian cyst should be guarded against because of the possibility of secondary implantations in the peritoneum.

7 Accurate classification of the mixed tumors is frequently impossible in the present state of our knowledge.

SUMMARY OF REPORTED CASES OF MALIGNANT OVARIAN TUMORS.

No.	Reporter	Age	Tumor	Reference
1	Brown, R.	9mo	Carcinoma	See reference to case No. 35.
2	Harris,	22	Endoth. Sarcoma	Am Jour, Obst. 1904, L, 530.
3	Flatau	22mo	Sarcoma	Münch. Med. Wochenschr. 1903, 532.
4	Hoffman and Keyser	33mo	Cystic sarcoma	Am. Jour. Obst., 1897, XXXVI, 331.
5	Evers	*yrs.* 2½	Sarcoma	St. Louis Courier of Med. 1884.
6	Gibb	2½	Myxo-chondro sarcoma	Glasgow Med. Jour. 1903, LX. 100.
7	Cameron	3½	Sarcoma	Glasgow Med. Jour. 1889 (4) S XXXI, 37–40.
8	Foerste	4½	Sarcoma	Am. Jour. Obst. 1896, XXXIII, 80.
9	Byford	4¾	Sarcoma	Chicago Med. Record 1891, II, 434.
10	Wiel	5	Carcinoma	Johns Hopkins Hosp. Bulletin, 1905, XVI, 102.
11	Viering	5	Sarcoma	See reference to case No. 31.
12	Page	6	Sarcoma	Lancet, 1895, II, 1622.
13	Turner	6	Sarcoma	See reference to case No. 31.
14	Cohn	6	Sarcoma	Ditto.
15	Croom	7	Sarcoma	Edin. Med. Jour. 1892–3, XXXVIII, 689.
16	Lucas	7	Sarcoma	Presse, Med. 2 Mai, 1888.
17	Amann, Jr	7	Endoth. Lymphaticum	Arch. f. Gynäk, XLVI, 493.
18	Gussenbauer	8	Carcinoma	Wiener Med. Wochenschr. 1894, 47.
19	Stolypinski	8	Sarcoma	See reference to case No. 31.
20	Chenoureth	8	Carcinoma	Ditto.
21	Leopold	8	Cystic Sarc.	Arch. für Gyn. VI, 189.
22	Olshausen	8	Carcinoma	See reference to case No. 31.

No.	Reporter	Age	Tumor	Reference
23	Malius	9 yrs	Cystic sarc.	Lancet, 1890, I, 1174.
24	Forbes	9 ..	Myxo-sarc.	Australian Med. Jour., 1894, XVI.
25	Tanner, J. H.	9 ..	Carcinoma	See reference to case No. 35.
26	Leopold	9 ..	Carcinoma	See reference to case No. 31.
27	McBurney	10 ..	Sarcoma	Annals of Surgery, 1895, XXI.
28	Emmett	10 ..	Malignant tumor	Am. Jour. Obst. July 1881, XIV, 674.
29	Wagner	10 ..	Sarcoma	Arch. für Klin. Chir. XXX, 504.
30	Klebs	10 ..	Carcinoma	See reference to case No. 35.
31	Hubert	11 ..	Endothelioma Lymphaticum	Ueber Ovarial Geschwültse bei Kindern, Giessen, 1901.
32	Halliday Croom	11 ..	Sarcoma	Obst. Trans. Edin. XIV.
33	Leopold	11 ..	Carcinoma	See reference to case No. 31.
34	Olshausen	11 ..	Carcinoma	See reference to case No. 31.
35	Kluge	11 ..	Sarcoma	Dissertation, Marburg, 1894.
36	Kelly	12 ..	Sarcoma	Keating's Encyclop. of Diseases of Children, 739.
37	Olshausen	12 ..	Carcinoma	See reference to case No. 31.
38	Wagner	13 ..	Sarcoma	Arch. für Klin. Chir. XXX, 505.
39	Wells	13 ..	Sarcoma	Diseases of Ovaries, N. Y. 1873, 56.
40	Martin	13 ..	Carcinoma	Krankheiten der Eierstöcke, 1899, 369.
41	Leopold	13 ..	Carcinoma	Gyn. Ges. Dresden, 12 Juli, 1894.
42	Leopold	13 ..	Sarcoma	Ditto.
43	Eckhardt	13 ..	Sarcoma	Deutsche Med. Wochenschr., 1895, Vereins Beilage, 14.
44	Demakis	13 ..	Carcinoma	Dissertation Göttingen, 1895.
45	Flaischlen	13 ..	Carcinoma	See reference to case No. 31.
46	Cohn	13 ..	Carcinoma	Ditto.
47	Mertens	13 ..	Sarcoma	Deutsche Med. Wochenschr., 1894, 96.
48	Bode	13 ..	Sarcoma	Gyn. Geselsch. Dresden. 12 July. 1894.
49	Schrooder	13 ..	Carcinoma	Zeitschr. für Geb. und Gyn. 1883, 9369.
50	Smith	14 ..	Sarcoma	Lancet, 1874, vol. II.
51	Leopold	14 ..	Sarcoma	Arch. für Gyn. VI.

No.	Reporter	Age	Tumor	Reference
52	Solger	14 yrs	Carcinoma	Beitrage zur Geburtshülfe und Gynäk, I, pg. 90.
53	Kaltenbach	14 ..	Carcinoma	See reference to case No. 31.
54	Muratoff	14 ..	Sarcoma	See reference to case No. 31.
55	Vonnegut	14 ..	Sarcoma	Dissertation, München, 1896.
56	Amann, Jr	14 ..	Endoth. Lympaticum	Gesellch. f. Geb. u. Gynäk zu München, 21 Jan. 1897.
57	Thornton	15 ..	Carcinoma	Med. Times & Gazette, London, 1883.
58	Dyonsten and Szabo	15 ..	Carcinoma	Arch. für Gyn. XXXII. 194.
59	Koeberle	15 ..	Carcinoma	Gaz. Med. de Strassburg, 1875.
60	Geyer	15 ..	Carcinoma	Dissertation, Würzburg, 1897.
61	Bergesio, L.	15 ..	Cysto-sarcoma	Osservatore Toreno, 1883, p. 529.
62	Hanks	15 ..	Cystic Carcinomatous Degeneration	Am. Jour. Obst., 1891, XXIV, 941.
63	Dembo	15 ..	Cystic Carcinamatous Degeneration	Dissertation, Berne, 1892,
64	Kratzenstein	15 ..	Sarcoma	Zeitschr. f. Geb. u. Gyn., XXXVI, 93.
65	Pick	15 ..	Sarcoma	Centralbl. für Gynäk 1894, 941.
66	Shatz	15 ..	Carcinoma	Corresp. Blatt. des Allg. Mecklenburg, Aerzte Vereins No. 106.

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ACTINOMYCOSIS LIMITED TO THE URINARY TRACT.

By E. MacD. STANTON, M. D.,

(From the Bender Laboratory, Albany, N. Y.)

Actinomycosis limited to the urinary tract is of exceedingly rare occurrence. In a careful search of the available literature on human actinomycosis, an instance of such localization has not been found. It seems advisable therefore to record a case in which an actinomycotic lesion was limited to the kidney and bladder.

Actinomycosis involving the kidney as an incidental lesion in the pyæmic form of the disease is by no means uncommon; cases of this type having been reported by Ruhrah,[1] Mallory,[2] Kobler[3] and others. Both the kidney and bladder may be involved by the direct extension of lesions originating in other organs, the most frequent source being the gastro-intestinal tract. Such cases have been reported by Billroth,[4] Bell[5] and others.

The case here reported was clinically one of cystitis and pyelonephritis. The actinomycotic character of the kidney lesion was not recognized during life or at the time of the autopsy; but was discovered only upon histological examination of the kidney. For this reason it has been impossible to definitely determine certain points which might have an important bearing on the unusual localization of the lesions.

REPORT OF CASE.

(Records of the Bender Laboratory, Autopsy No. 839.)

Clinical history. Mr. W., white, aged 53, shoemaker, admitted to St. Peter's Hospital, January 7, 1905, service of Dr. Henry Hun.

Family history. Negative.

Personal history. Always healthy. Uses alcohol to excess. Denies venereal history.

Present illness. About two months before admission to the hospital the patient began to have difficulty in passing his urine. He could pass only a small amount at one time and the stream was small. For some time before admission he had been troubled with dribbling of urine over which he had no control. The passage of urine caused a burning sensation.

Physical examination. Patient well developed. Pupils unequal, the left being irregularly dilated. Tongue enlarged, flabby, has fine tremor and is covered with white fur. Lungs resonant. Expiratory murmur prolonged. Heart sounds rather faint but otherwise normal. Abdominal examination negative. Bladder somewhat distended. Knee jerks present.

Urinary examination. January 8th, specific gravity 1020; acid; cloudy; trace of albumen; no sugar; many leucocytes and epithelial cells. January 23rd, specific gravity 1010; acid; cloudy; many pus cells.

Blood examination. January 23rd, haemoglobin 45 per cent.; leucocytes 6000.

Sputum examination. Many encapsulated diplococci. No tubercle bacilli found.

While in the hospital the patient ran an irregular temperature ranging from 99 to 103 and was slightly irrational the greater part of the time. In addition to the bladder symptoms he had a slight cough.

The treatment was purely symptomatic and consisted of cystogen in five grain doses every four hours together with a cough mixture, bismuth subnitrate, tannigenfi, strychnine and digitalis.

Autopsy. Made by Dr. Stanton eighteen hours after death.

The body is that of a large framed, poorly nourished adult male. Length of body 167 centimeters. Rigor mortis present. No œdema. Pupils unequal. Skin of a uniform yellow color except for moderate reddish discoloration of dependent parts. On the outer aspect of the right thigh 6 centimeters below the crest of ilium is an irregular, depressed reddish scar.

Abdominal cavity. No free fluid. Serous surfaces smooth and glistening. The omentum covers the intestines, is rich in fat and adherent by fibrous adhesions to the left side of the urinary bladder. The appendix points downward and its tip is adherent to the bladder. The transverse colon is adherent to the gall-bladder by a few fibrous bands.

Pericardial cavity. Negative.

Pleural cavities. Negative except for a few fibrous adhesions at both apices and at base of left lung.

Heart. Normal in size; pericardium and endocardium normal. Valves negative except for slight thickening at attached borders of aortic valves. The myocardium is firm and brownish red in color. Wall of left ventricle averages 14 to 16 millimeters in thickness.

Right lung. Surface smooth. On section numerous yellowish caseous nodules 1 to 5 millimeters in diameter are found at the apex, while in the middle lobe are many closely arranged recent tubercles 2 to 4 millimeters in diameter. These have a distinctly peribronchial arrangement. The lower lobe contains many similar nodules. Lung otherwise negative except for moderate carbon pigmentation.

Left lung. Pleural surface smooth except at apex and along posterior surface where there are a few fibrous tags. The apex is puckered containing a distinctly encapsulated caseous nodule 1 centimeter in diameter surrounded by a number of small firm nodules. Scattered throughout the remainder of the lung are nodules similar to those in the right lung.

Spleen. Weight 240 grammes; capsule smooth; cut surface dark red in color; trabeculæ distinct; follicles indistinct.

Liver. Weight 1500 grammes. The capsule is normal except for a few thickened slightly wrinkled areas on the upper anterior surface of the lower lobe. On section the cut surface shows red and greyish yellow mottling; the darker areas correspond to the centres of the lobules. Gall-bladder and ducts normal.

Gastro-intestinal tract. The stomach is dilated; its mucosa smooth, pale and covered with a thick tenacious mucus. The remainder of the gastro-intestinal tract is negative except for a small pit-like depression in the middle of the transverse colon which represents apparently a healed ulcer.

Right Kidney. Weight 230 grammes. The capsule strips with some difficulty leaving an exceedingly pale greyish-yellow cortex with deeply injected stellate veins. On section the pelvis is filled with a thin greyish yellow purulent fluid. The pyramids and adjacent cortex are streaked by greyish yellow lines of purulent infiltration. In many places the areas of suppuration are confluent, forming abscesses 0.5 to 1 centimeter in diameter filled with a thick pus containing fragments of necrotic tissue. The ureter contains a thin cloudly fluid.

Left kidney. Weight 160 grammes. The capsule strips with some difficulty leaving a coarsely lobulated pale yellow surface. On section the cortex is seen to be markedly thinned. The cut surface is pale yellow in color and has a glistening appearance. The iodine test for amyloid is negative. Ureter normal.

Urinary bladder. The wall is very greatly thickened and is firmly bound to the pelvis on the right, posteriorly, by dense connective tissue containing islands of fatty tissue. On removing bladder numerous pus cavities are opened, a thick yellow pus escaping. The mucosa of the bladder which shows irregular losses of substance is slightly granular and has a mottled greyish yellow color. The cavity of the bladder is filled with a thick mucoid pus and many of the pus-containing pockets opened in removing the bladder are found to communicate with the bladder being, apparently, diverticula.

Prostate, seminal vesicles and *testicles.* Normal.

Adrenals. Normal.

Aorta. Normal.

Anatomical diagnosis. Chronic ulcerative cystitis. Suppuration in diverticula of bladder. Chronic pericystitis. Pyelo-nephritis (right). Chronic diffuse nephritis. Pulmonary tuberculosis. Fatty liver with slight chronic passive congestion. Scar of right hip. Scar of old ulcer (?) in colon. Chronic peritonitis. Chronic pleuritis.

Bacteriology. Cultures from right kidney sterile after 48 hours.

Histologic examination—Lung. Sections through nodular masses show tubercles made up of epithelioid cells, giant cells and lymphocytes and with central areas of caseation in and about which are slender beaded bacilli which stain by the Gabbet and Gram-Weigert methods. Careful examination of many sections revealed no evidence of the presence of actinomyces or other streptothricial forms.

Left kidney. A few small focal areas in cortex show increase of interstitial tissue with an occasional hyaline glomerulus. Other glomerular tufts in these areas are shrunken and lobulated with wide intra-capsular spaces. The cells of the convoluted tubules are swollen and granular. A few hyaline casts are seen in the straight tubules.

Right kidney. Same chronic changes as in left kidney. In addition sections taken through the abscesses in the pyramids and cortex show irregular areas of suppuration. These areas are composed of polynuclear leucocytes and cell detritus in the midst of which are seen numerous typical actinomyces colonies with well developed "clubs." The persisting kidney tissues about such areas are diffusely infiltrated with lymphocytes, plasma cells and polynuclear leucocytes, while surrounding some of the larger abscesses there is a poorly defined zone of highly cellular newly-formed fibrous tissue. In the diffusely infiltrated areas the glomeruli and a large proportion of the tubules can still be made out. The mucosa and submucous tissues of the pelvis are infiltrated with lymphocytes, plasma cells and fibroblasts. A variety of staining methods, including those for the tubercle bacillus, prove the actinomyces to be the only organism present.

Bladder. Sections through the ulcerated portions of the bladder wall show an entire absence of epithelium. The mucosa is replaced by granulation tissue which is exceedingly rich in spindle shaped cells. On the surface of this tissue is a layer of partially necrotic cellular material containing a moderate number of leucocytes together with large clumps of cocci and a few bacilli. Small areas of necrosis extend into the deeper tissues of the bladder wall. The muscular coat shows a very marked increase of connective tissue of a highly cellular type. Although sections cut from a large number of blocks representing various portions of the bladder wall were examined for actinomyces neither colonies nor filaments could be found. Stains for tubercle bacilli are also negative.

Histologic diagnosis. Actinomycosis of right kidney. Chronic ulcerative cystitis with extensive formation of granulation tissue. Slight chronic diffuse nephritis. Pulmonary tuberculosis. Old blood pigment in spleen. Congestion and fatty metamorphosis of liver.

The presence of colonies of actinomyces in the kidney abscesses leaves no doubt as to the nature of the renal lesion. The failure to find either colonies or filaments of actinomyces in the bladder wall, however, raises a question concerning the character of the bladder lesion. On the other hand the presence of actinomycosis of the kidney and the peculiar character of the histological changes in the bladder wall indicate the probability that this lesion also is actinomycotic in nature.

The mode of infection in this case is doubtful and it is more than possible that the lesion in the urinary tract was secondary to a primary focus which had existed in some other part of the body but which had disappeared at the time of autopsy. The small scar-like area in the colon, the various peritoneal adhesions and the old scar on the outer aspect of the right thigh each suggest antecedent inflammatory conditions offering possible routes of infection; but no connection could be traced between any of these and the lesion in the urinary tract. The presence of tubercle bacilli in the lung and the absence of actinomyces dispose of any possibility that the lung lesion might have been the portal of infection.

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BENDER HYGIENIC LABORATORY.

Annual Report of the Director, for the Year Ending August 31, 1905.

BY RICHARD M. PEARCE, M. D.

To the Trustees of the Bender Hygienic Laboratory:

I have the honor to submit my report for the year ending August 31, 1905.

The Work of the Laboratory. This may be conveniently divided into routine examinations, under-graduate teaching, instruction to special students and original investigation.

The nature of the routine work of the laboratory is shown in the accompanying table which gives the source of the material and the number and character of the examinations. Mr. Wachter's tabulation of his chemical and bacteriological examinations, made at the filtration plant, have been included in his annual statement to the Water Bureau of the City of Albany and do not appear in this report.

TABULATION OF THE ROUTINE EXAMINATIONS MADE BY THE STAFF OF THE BENDER LABORATORY FROM SEPTEMBER 1, 1904, TO AUGUST 31, 1905.

	State Dept. of Health.	City Board of Health.	Albany Hospital.	St. Peter's Hospital.	Ellis Hospital, Schenectady.	Child's Hospital and St. Margaret's House.	Albany Orphan Asylum.	Coroner's Physicians.	All other sources.	
Autopsies	....	....	30	3	3	21	4	28	40	129
Surgical specimens	....	....	945	184	61	5	1	....	75	1,271
Throat cultures	888	407	....	....	....	....	....	....	....	1,295
Sputum	458	45	1	....	....	1	....	....	30	535
Widals	143	....	86	17	....	2	1	....	39	288
Water, milk and ice	376	....	....	....	....	....	....	....	32	408
Miscellaneous	7	....	65	11	....	5	1	....	68	157
	1,872	452	1,127	215	64	34	7	28	284	4,083

These figures show a very satisfactory increase in the work in pathology, but a slight decrease in the number of bacteriological examinations. There is, however, an increase over last year of three per cent. in the total number of examinations. The greatest increase has been in the number of surgical specimens, which show an increase of 26.7 per cent. over last year. This is largely due to the fact that the laboratory now does the work of the St. Peter's Hospital, of Albany, and the Ellis Hospital, of Schenectady.

The laboratory courses during the past year (term of seven and a half months) to undergraduates of the Albany Medical School were as follows:

Pathology and bacteriology.—Drs. Pearce, Stanton, Winne and Sibley, eight and a half hours a week.

Normal histology.—Drs. Stanton and Boyd, six hours a week.

Clinical microscopy.—Drs. Laird and Sibley, two and a half hours a week.

Surgical pathology.—Drs. Elting and Carey, two and a half hours a week.

Histology and pathology, in connection with the course in obstetrics.—Drs. Lipes and Boyd, two and a half hours a week.

Anatomy and pathology of the nervous system.—Drs. Stanton and Boyd, one and a half hours a week.

In connection with the course in pathology the most serious need is some arrangement by which post-mortem examinations may be made before the entire class. At present, this instruction can be given only to small sections at irregular intervals. It would appear possible, by combined action of the Albany Hospital, the faculty of the Albany Medical College and the trustees of the Bender Laboratory, to arrange for proper facilities at the Albany Hospital. I respectfully suggest to the trustees the necessity of immediate action upon this question.

Physicians who have availed themselves of the opportunity to work in the laboratory for considerable periods of time are Dr. R. Fletcher Van Heusen of San Francisco, Dr. Ellice McDonald of New York, Dr. C. G. McMullen and Dr. W. P. Faust of Schenectady, and Drs. J. A. Cox, J. A. Lanahan, J. A. Sampson, J. F. Rooney, A. J. Douglas, A. T. Hull and K. D. Blackfan of Albany. Undergraduates having similar privileges were Messrs. J. L. Donnhauser, Erastus Corning, Jerome Myers, E. W. Jackson, J. H. Linden, J. F. Robinson, S. P. Brush, R. A. Lawrence and F. C. Conway, students of the Albany Medical School, and Mr. Nelson Fromm, of Dartmouth Medical College. These gentlemen have assisted in the routine work of the laboratory, pursued special lines of study or engaged in research work.

Investigations completed during the past year are as follows:

1. STANTON, E. MACD., The Sequence of the Pathologic Changes in Appendicitis.—*Journal of the American Medical Association, 1905, xliv, 1849.*
2. BALDAUF, LEON K., Cancer of the Appendix Vermiformis, with Report of Three Cases.—ALBANY MEDICAL ANNALS (*in press*).
3. CORNING, E., Retention Cyst and Diverticulum of the Appendix Vermiformis.—ALBANY MEDICAL ANNALS (*in press*).
4. LAIRD, A. T., The Elimination of Endogenous Uric Acid in Cases of Chronic Gout.—*American Medicine, 1905, x, 315;* ALBANY MEDICAL ANNALS, xxvi, 742.
5. PEARCE, R. M., Experimental Cirrhosis of the Liver.—*Journal of Experimental Medicine* (*in press*).
6. PEARCE, R. M., and STANTON, E. McD., Experimental Arteriosclerosis.—*Journal of Experimental Medicine* (*in press*).
7. STANTON, E. McD., Actinomycosis Limited to the Urinary Tract.—ALBANY MEDICAL ANNALS, xxvi, 738.
8. DONHAUSER, J. L., Malignant Ovarian Tumors in Children with Report of a Case.—ALBANY MEDICAL ANNALS (*in press*).
9. McDONALD, E., The Various Forms of Puerperal Sepsis with Report of Cases.—*American Medicine* (*in press*).

Other investigations not yet completed are:

A Study of the Effect of Haemolytic Sera upon the Blood and Blood-forming Organs by Dr. C. K. WINNE, Jr; A Study of the Action of Toluylendiamin upon the Blood and Blood-forming Organs by Mr. J. L. DONHAUSER; and a Study of Sarcoma of the Uterus by Dr. ELLICE McDONALD.

The expense of the experimental work has been defrayed by a grant from the Rockefeller Institute for Medical Research; a similar grant has been obtained for the ensuing year.

LABORATORY CLUB. During the past year an organization known as the Laboratory Review Club has been formed. This includes the regular staff and all instructors giving courses in the laboratory. Its object is to cover, in the form of general reviews, a few of the important lines of work in scientific medicine. These reviews are afterwards published in the ALBANY MEDICAL ANNALS. Physicians and students doing special work in the laboratory are invited to attend these meetings so that an average attendance of twelve to fifteen has been the rule. This club has been so enthusiastically supported by all members and its advantages are so evident that it will be made a permanent organization.

CHANGES IN THE STAFF. Dr. E. MacD. Stanton and Dr. Chas. K. Winne, Jr., who were reappointed as regular assistants, and Dr. E. F. Sibley, who volunteered as assistant without salary for one year, have constituted the laboratory staff for the past twelve months. To the conscientious and earnest efforts of these gentlemen is due in large part the present efficiency of the laboratory in all lines of work. To Dr. Sibley we are especially indebted for time and labor given without substantial recompense. Dr. Stanton, having received an appointment at the St. Mary Hospital of Chicago, resigned in June. Dr. Leon Kahn Baldauf (Johns Hopkins University, A. B., 1901; M. D., 1905) has been appointed his successor. Dr. Winne resigned September 1st to enter private practice in Albany and in his stead Dr. Kenneth D. Blackfan (Albany Medical College, M. D., 1905) has been appointed. On September 1st, Dr. Sibley also terminated his connection with the laboratory in order to become an assistant to Dr. A. W. Elting.

The great increase in all departments of our work has led to the creation of three new positions. The first of these, an assistantship in Neuro-Pathology, was made possible through the generosity of Dr. Henry Hun. To this position has been appointed Dr. La Salle Archambault (Albany Medical College, M. D., 1902), who enters upon his duties after two years special study of neurology in the laboratories and clinics of Europe. The second position, that of assistant in Surgical Pathology, is the result of the generous cooperation of Drs. Albert Vander Veer and Willis G. Macdonald. To this position has been appointed Dr. Harold Eugene Robertson (Carlton College, A. B., 1899; University of Pennsylvania, M. D., 1905).

The third new position, that of Pathological House Officer to the Albany Hospital, is the natural result of the great increase in laboratory work of the latter institution. Although the incumbent of the position is appointed by the Board of Governors of the Albany Hospital at the recommendation of its staff, and is therefore an officer of the hospital, it appears justifiable, as the greater part of his work will be in the Bender Laboratory, to consider him as an assistant in the latter institution. Dr. William M. Dwyer (Albany Medical College, M. D., 1905) has been appointed by the Board of Governors of the hospital to fill this position during the year ending June 1, 1906.

The influence which these changes will have upon the work of the laboratory cannot be estimated. The staff for the past two years has been quite inadequate. The great variety and amount of our routine work including as it does, teaching, examinations for state and city boards of health, the autopsy work and the examinations of the surgical material of the various hospitals of this vicinity and the prosecution of special investigations has taxed the staff to its utmost and not infrequently has caused considerable embarrassment. Such difficulties, however, will be avoided by this increase in the staff.

Through financial assistance afforded by the Albany Medical College, the janitor service has been increased and this very important service is now highly satisfactory.

Mr. Leonard M. Wachter was reappointed for the year 1905-'06 as assistant chemist and bacteriologist, in charge of the Albany filtration plant.

Improvements, Repairs, Etc. These have been entirely practical and are not of great importance. The small room off the large class room has been transformed into a museum. Here has been formed the nucleus of a museum of gross pathology. On the first floor new quarters have been built and furnished for the janitor. Speaking tubes and call bells have been installed, thus obviating much unnecessary confusion and expediting the work. A set of framed bacteriological plates have been placed in the class room. During the past summer the usual amount of repairing, painting and varnishing of woodwork has been done. The building is in excellent condition and I have now nothing to suggest in the way of repairs or improvements.

Of great advantage has been the space regained by the removal of the State Antitoxin Laboratory. Of the four rooms thus vacated two are now devoted to general laboratory purposes, one has been fitted up as an operating room and the fourth has been reserved for Dr. H. C. Jackson, recently appointed Adjunct Professor of Physiological Chemistry in the Albany Medical School. Although Dr. Jackson's classes will be held in the new laboratory at the Medical School buildings, it seems advisable, owing to the many advantages offered by the Bender Laboratory and also on account of the proximity to the city and county hospitals, that space and facilities for research work be given him in this laboratory.